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CLINICAL RESULTS WITH THE USE OF AGGLUTINOGEN FROM PHASE I HEMOPHILUS PERTUSSIS AS A SKIN TEST FOR SUSCEPTIBILITY TO WHOOPING COUGH

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PRELIMINARY studies on the preparation and use of the purified agglutinogen of phase I *Hemophilus pertussis* as a skin test for susceptibility to whooping cough have been described by Flosdorf and associates.[1-6] The results obtained in the early studies on animals and human beings have been repeated in further trials in human beings. The results of this detailed clinical study are now presented.

The antigenic structure of *H. pertussis* includes an agglutinogen and apparently two toxins; one toxin is thermolabile, the other thermostable. The agglutinogen produces an allergic type of skin reaction in immune or partially immune individuals, whereas the toxins give a more delayed positive reaction in susceptible individuals. In the past, results of skin testing for susceptibility were not entirely satisfactory because the preparations used contained both toxin and agglutinogen so that confusing and overlapping results were obtained. More recently, a skin test has been described by Strean and co-workers[7] using purified toxin. Strean's results indicate that it is not possible, by this test, to distinguish between the susceptible individuals and those who have been immunized with killed whole phase I organisms.

Vaccines of killed whole phase I organisms containing no thermolabile toxin produce a substantial degree of immunity in children as shown by Sauer,[8] Kendrick and Eldering,[9] Miller and Faber,[10] Singer-Brooks,[11] and others. This immunity can be shown to be related to the antibacterial antibodies which result. In individuals recovered from whooping cough, the same antibodies can be demonstrated. It would seem, therefore, that the agglutinogen component of *H. pertussis* would afford a logical reagent to react intradermally with these antibodies to determine immunity or susceptibility.[1, 4]

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The agglutinogen prepared in such a way that it is free of toxin[1] has been extensively studied in the laboratory.[1, 2, 12] Massive doses produce no histopathologic changes[12] in rabbits, whereas very small doses of preparations containing one or both of the toxins show marked changes. It is felt, therefore, that the agglutinogen is a safe reagent.

The agglutinogen is standardized in terms of arbitrarily chosen units based on assay by absorption of agglutinins from immune serum.[13] One unit contains approximately 2 to 3 gamma of solids. The material is probably protein in nature.[1] Ten units in 0.1 ml. of 0.85 per cent sodium chloride have been used as the test dose in this study.[3, 6]

RESULTS

In children with a definite history of pertussis or vaccination against it, unmistakable reactions were obtained. In normal babies between 6 and 14 months of age with no histories of the disease or vaccination, no reactions resulted from skin tests with purified agglutinogen. The normal babies were chosen from the age group of 6 to 14 months, because the histories could be more accurately obtained and the very mild cases which occur often undiagnosed in older children were avoided. In infants over six months of age, the skins reacted reliably. There were certain children over 14 months of age with no known history of the disease or vaccination who gave weakly positive reaction. This may have been due to a contact immunity or a subclinical infection.

Apparently two types of response were obtained: the immediate, or wheallike, reaction, and the delayed, or tuberculin, type of reaction. Some of the immune children showed both, some one or the other. In order to evaluate the reaction, two readings were made,[3, 6] one-half hour and twenty-four hours after injection.

In order to simplify the interpretation of the reactions, they were graded in the following way:[6]

P-I—Positive-Immune
A well-indurated reaction (with or without erythema) 20 mm. or more in diameter at either one-half hour or twenty-four hours or both.
WP-I—Weakly Positive-Immune
An indurated reaction (with or without erythema not exceeding 20 mm. in diameter at either one-half hour or twenty-four hours, but at least 10 mm. in diameter at either time or both.
N-S—Negative-Susceptible
No indurated reaction at either one-half hour or twenty-four hours beyond an area 10 mm. in diameter

Induration was the determinant factor between a weakly positive-immune reaction and a negative-susceptible reaction. An area of 10 mm. was considered as the upper limit for negative reactions, because certain normal skins gave a slight response to the trauma of the injection. In no case was there any untoward local or systemic effect. The reaction faded quickly and usually disappeared in thirty-six hours or sooner. In Negro children, immune or susceptible, there usually was some residual pigmentation, which is not abnormal in this race.

The results of testing 776 children are summarized in Table I. Ninety-four babies provided the normal control group. None of these babies had any reaction to the skin test. The negative-susceptible reactions in this group of babies present, perhaps, the most significant finding in this study.

TABLE I

RESULTS OF INTRADERMAL TESTING WITH PURIFIED PHASE I AGGLUTINOGEN

CLASSIFICATION	TOTAL NUMBER	N-S	WP-I	P-I
Normal babies 6 to 14 months old	94	94	0	0
Vaccinated	305	23*	112	170
History of pertussis (not bacteriologically diagnosed)	113	21	38	52
Unknown history	264	61	85	118
Total	776	199	235	340

N-S, Skin test susceptible (negative).
WP-I, Skin test slightly immune (weakly positive).
P-I, Skin test immune (positive).
*These children received a vaccine of questionable potency.

Three hundred and five children were included in the vaccinated group. Among these were 225 from an institution in which the children had all received a vaccine determined later to be of questionable potency. Most of the negative-susceptible reactions of the vaccinated group were in these children. Also included in this vaccinated group were twenty-six children from the clinics of the Children's Hospital of Philadelphia. The records showed that these children had all been given the recommended dose of vaccine of killed whole phase I *H. pertussis* organisms, from three months to as long as five years before the skin testing was carried out. None of the negative-susceptible reactions reported were seen in these children.

The children recorded as having had the disease were principally from the institutions to which we had access. The children in these institutions were convalescents whose available histories were summaries of a previous hospitalization. The data, therefore, were not always as accurate as if they had been obtained from the original source. A few of the children had been diagnosed in the clinic of the Children's Hospital of Philadelphia from six months to ten years before testing. In no instance had there been a bacteriologic diagnosis.

Many of the skin tests were checked with serum agglutinations against phase I *H. pertussis*. There is a definite correlation between the intensity of reaction and the height of the titer as summarized in Table II. It is not surprising that many of the individuals tested gave a positive skin test reaction without the presence of circulating antibodies, since obviously fixed antibodies may be present in the absence of circulating antibodies. In only one case where a positive agglutination test was obtained did the skin test indicate susceptibility.

TABLE II

RELATION OF AGGLUTINATION TITER AT TIME OF TEST TO TYPE OF SKIN REACTION

REACTION										
Skin test Immune (Positive)	47	9	3	10	5	8	10	3		
Skin test Slightly Immune (Weakly Positive)	18	3	3	5	5	2	1			
Skin test Susceptible (Negative)	40			1						
Titer	0	1:20	1:40	1:80	1:160	1:320	1:640	1:1280	1:2560	1:5120

It was possible to get samples of blood from many of the children some time after the skin test. The antibody response observed three weeks after the skin test was unusually great.[3, 5] These results are summarized in Table III. The last column in Table III shows the number of cases in which the titer had risen from zero to a definite value, as high as 1:10,240 in some instances. This number includes all of the children who had a positive-immune or weakly positive-immune test and no agglutinating titer at the time of the test. This indicates that in those individuals having only fixed antibody initially, there was a marked production of circulating antibody. From many of these children it was possible again in three months to obtain blood. The increased titers observed three weeks following the test had been maintained undiminished in virtually every case for the three-month period.

TABLE III

ANTIBODY RESPONSE IN THREE WEEKS TO A SINGLE INTRADERMAL DOSE

NUMBER OF PATIENTS SHOWING NO INCREASE IN TITER	FACTOR OF INCREASE AMONG PATIENTS WITH AN INITIAL TITER									NUMBER OF PATIENTS SHOWING INCREASE WITHOUT INITIAL TITER	TOTAL
	2^1	2^2	2^3	2^4	2^5	2^6	2^7	2^8	2^9		
* 24 ‡	3	3	2	8	2	2	3	2	0	† 52	101

*Two of these had an initial titer of 2,560 or higher (close average maximum ceiling).

†The initial titer was zero, but in every case the skin test was P-I or WP-I.

‡Fourteen of these had zero initial titer and N-S skin test reaction. Repeated intradermal tests in such cases are required to produce a titer and to reverse the skin test.

The cases in the first column in Table III represent the children who had no increase in serum titer of agglutinin after the skin test. Fourteen of these had negative-susceptible reactions and no agglutinins to *H. pertussis;* the remainder were positive-immune with an initial agglutinin titer close to the average maximum ceiling. In no case in

which an individual had a negative-susceptible reaction was there an antibody response to the single intradermal skin test injection sufficient to reverse the test and to produce a detectable titer of circulating antibody. It was shown in a small series, however, that it was possible to reverse the skin test and to produce a detectable titer of circulating antibody, by repeated intradermal doses of agglutinogen in those individuals giving a negative-susceptible reaction at the time of the first test. Usually three such intradermal doses were required in order to produce such a rise in titer. The agglutinin titers were determined again in this small group six months following the final injection, and it was found that the titer had not diminished.

Careful study of a small institutional epidemic indicated that immunity is accurately shown by skin testing with purified agglutinogen. It was found in this study also that where immunity exists, as determined by skin testing and by agglutinin titers, it is greatly increased as a result of the stimulus of the small intradermal dose used. The increase in the agglutinin titer was found to have been maintained in all cases when tested three months later. This type of investigation is being continued.

DISCUSSION

The results of the early use of the purified agglutinogen as a skin test formed a definite pattern which has not varied in subsequent studies. The marked rise in agglutinin titer to *H. pertussis* following skin testing suggests[3, 5] that the material may serve as a "stimulation" or "step-up dose" in individuals who have an existing immunity or partial immunity to whooping cough. The small series in which it was possible to produce both an agglutinin titer and reversal of the skin test, by repeated doses, seems to indicate that the material might also prove to be a valuable primary immunizing agent.

The small institutional epidemic which was mentioned afforded an opportunity to determine the practical value of this skin test. The results were very encouraging. The actual value of the material, however, will not be known until it has been used over a long period of time in large groups on whom accurate epidemiologic studies can be made under controlled field conditions.

The agglutinogen used in this study was prepared from organisms grown on medium containing horse blood. Ordinary laboratory methods using complement fixation and precipitin tests showed no trace of any of the components of the medium. It is quite possible that minute amounts of horse serum protein still may have been present in the test material. In the first one hundred and fifteen cases, a parallel control test was made, using a 1:700 dilution of horse serum. There were no reactions to this control material in the group tested. Subsequently, however, three individuals gave positive-immune reactions when the history indicated susceptibility. These individuals gave comparable

reactions when tested with the dilute horse serum. The use of human blood in the culture medium would eliminate the possibility of such occasional reactions to horse serum protein.

SUMMARY

The results of a clinical study, using the purified agglutinogen of phase I *Hemophilus pertussis* as a skin test for susceptibility to whooping cough, are presented. The test seems to classify immune and susceptible individuals according to their histories, both of disease incidence and vaccination, in a satisfactory way. In addition to its use as a skin test, the agglutinogen in single skin test doses produces a marked increase in the titer of individuals with existing immunity or partial immunity to pertussis. Repeated doses produce a reversal of the test and a titer in those with no initial immunity. Careful study of a small institutional epidemic indicates that susceptibility can be predicted by the use of this skin test.

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OBSTRUCTIVE EMPHYSEMA AND ATELECTASIS IN TUBERCULOSIS OF INFANTS AND CHILDREN

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IT IS the purpose of this paper to describe a group of tuberculous children in whom mechanical effects of the disease process were responsible for the major, and usually the only, evidences of illness. The effects to be described have been confined to various portions of the lungs and have, in general, been either atelectasis or emphysema; the mechanisms themselves are either known to have been endobronchial obstructions or suspected to have been pressure effects of infected tissues adjacent to the bronchi.

In most infants and children with a tuberculous primary focus the extent of its lymph node portion exceeds that of the area of primary lung infection, and in some cases the preponderance of lymph node disease may be extreme. The anatomic association of these nodes with the bronchi offers an obvious opportunity for mechanical interference with respiration. Such interference may not be entirely from the glands alone. Hughes and Simpson[1] recently have summarized what may happen. Simple external compression, ulceration through the bronchial wall, the formation of a mural mass of tuberculous granulation tissue, and finally actual cicatricial stenosis of the bronchus may occur, either as individual entities or in various combinations. Additional nontuberculous factors, such as excessive tracheobronchial secretion accumulating below the obstruction, and nonspecific infections may play some part in the total process. Whatever the form of obstruction, its result upon the associated lung will depend, in general, upon its degree. Partial obstruction large enough to have any effect tends to produce obstructive emphysema by allowing the ingress of air during inspiration but preventing its outflow by completely blocking the somewhat lessened bore of the bronchus during expiration.[2] Complete obstruction of any sort produces atelectasis by allowing the air in the lung beyond it to be absorbed but not replaced. It is possible for either of these conditions to exist without much embarrassment to the patient, and therefore, as Spivek[3] has pointed out, it is difficult to state the actual incidence of bronchial obstruction from tuberculous lesions. His review of the literature disclosed fifteen patients with "typical" cases of pulmonary emphysema reported by various authors as due to this cause, and he added four instances observed by himself. Five years later, in 1941, Barsby[4] de-

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scribed three children with partial or complete obstructive emphysema of an entire lung, which was considered the effect of tuberculous hilar nodes.

Much of the literature dealing with atelectasis in tuberculosis of childhood describes the role of atelectatic processes in producing bronchiectasis,[5] while several authors have considered the possible relationship between atelectasis of this nature and the so-called "epituberculosis."[6] A few single cases of atelectasis as a purely mechanical incident have appeared.[7] The impression gained from the literature is that atelectasis, perhaps even more than emphysema, is of comparatively rare occurrence but that it may more often lead to serious consequences.

In the past eleven years there have been observed at the Infants' and Children's Hospitals fifteen patients in whom either obstructive emphysema or atelectasis has been discovered in association with a primary tuberculous infection which probably or certainly involved the hilar region. So varied has been the resultant clinical picture and so generally satisfactory has been its outcome in the face of rather alarming possibilities that we have felt it worth while to present the following brief reports and discussion of our experience with this group of patients.

CASE REPORTS

CASE 1.—D. T. (242909), a boy 1 year of age, was admitted to the hospital in June, 1940, with the following story: During the first two weeks of life he was heavily exposed to tuberculosis.[8] At 7 months of age he had had a severe episode of wheezing and difficult breathing. At this time there was also some diarrhea, anorexia, and vomiting. At 11 months of age he again began to cough severely and to have difficult wheezing respiration. After these symptoms had continued for a month with a temperature ranging between 100 and 100.4° F., examination showed good development and nutrition and no outward appearance of illness. Nothing specific was found on physical examination of the chest. The liver and spleen were palpable. A roentgenogram showed emphysema of the right lung, particularly in the middle and lower portions, compensatory to atelectasis of the right lower lobe. Tuberculin test was positive. The patient remained in the hospital for twenty-two days, during which time he continued to have a good deal of cough but no further elevation in temperature. Repeated roentgenograms showed the emphysema and atelectasis to clear within about six weeks after his discharge, so that the process probably persisted for about two months in all.

In March, 1942, about twenty months after the first admission, the child was readmitted to the hospital for study of another complaint, and a roentgenogram at this time showed no evidence of active tuberculosis or mechanical disturbance of aeration in the lungs.

CASE 2.—E. L. (256323), was born on May 28, 1941, to parents who are supposedly free from any chronic disease. In September, 1941, at the age of 5 months, the infant developed what her mother described as a "heavy bronchitis." This consisted mainly of frequent cough, but there was no mention of wheezing or of difficulty in breathing. These symptoms gradually disappeared after lasting for about one month. In October, 1941, films of the right shoulder, which were taken because of possible fracture, included enough of the chest to show an area of hyperaeration in the right middle lung field. The child escaped attention until

the end of February, 1942, when, at the age of 9 months, she was brought in because of eczema. At that time there was no cough, and there were no physical signs in the chest, but roentgenograms showed the same hyperaeration in the upper portion of the right upper lobe above an area of increased density in the lower portion of this lobe. The appearance suggested a partial atelectasis which could possibly be due to tenacious secretions, a foreign body, or pressure from an external mass upon a bronchus. A definitely positive reaction was obtained to 0.1 mg. of old tuberculin. A third roentgenogram done one week after the second showed slightly less interference with the aeration of the lower portion of the right upper lobe. The child has not yet been examined by bronchoscopy or with lipiodol, but it seems probable that the obstruction to a portion of the right lung is due either to tuberculous granulation tissue in the bronchus leading to that area or to pressure from enlarged mediastinal lymph nodes or pulmonary infiltration upon this bronchus.

CASE 3.—R. M. (207142), aged 11 months, came into the hospital in October, 1935, because of severe cough for two weeks. There had been considerable contact with tuberculosis. The child had done well until six months before entry when he had had a bad cold for a week with fever which suggested pneumonia. Since that time he had wheezed a great deal, so that two months before entry roentgenograms were taken at another hospital. These were brought with him; they showed atelectasis of the right and left upper lobes with some shift of the mediastinum toward the left side.

The symptoms persisted, and a cough suggesting pertussis caused him to be taken to another doctor who sent him to this hospital. Physical examination showed a fat little baby in no apparent distress. Breath sounds were greatly diminished throughout the right lung, a slightly hyperresonant note was heard on the right posteriorly, and a slight impairment of resonance at the right apex in front. No râles were heard. Reaction to 0.01 mg. of old tuberculin was positive. The x-rays now showed atelectasis of the right middle lobe and marked emphysema of the right lower. It was felt that the child now had collapse, mainly of the middle lobe, with compensatory increased size of the rest of the right lung, and probable pressure of enlarged nodes at the right bronchus to bring about these circumstances. Gastric contents were examined for acid-fast organisms, and definite bacilli of this type were found in considerable numbers in a concentrated specimen. The temperature averaged between 98.6 and 99° F., but on one occasion rose to 100.2° F. The child remained in the hospital for only one week and was sent home, unchanged, to his family physician, who writes three and one-half years later that the child appears to be in perfect health, although no x-rays have been taken.

CASE 4.—M. C. (17622), an infant girl of 8 months, entered the hospital with the story of a severe cold for three weeks, with difficulty in breathing during the last few days. She remained on the ward for four months, during the last of which occurred the events which are most significant for this report. At first she had a course of intermittent fever and changing pulmonary signs suggestive of bronchopneumonia, and at one time a definite area of consolidation was shown in the left upper lobe. The tuberculin test was positive, but it was difficult to decide whether the process was entirely tuberculous or was a pyogenic chronic pneumonia. Tubercle bacilli could not be demonstrated in the stomach washing. One blood culture contained streptococci, but many others were negative. The blood counts were not helpful. During the third month in the hospital, cervical adenitis occurred, and finally a gland was excised which proved by section to be tuberculous in nature. During the fourth month coughing became much worse, dyspnea was marked, breath sounds were absent over the entire left side, and the heart was pushed to the right. X-rays showed a marked left-sided emphysema with depression of the diaphragm.

Bronchoscopy was performed by Dr. Charles Allman on the next day, but nothing was found except for an appearance of decrease in the diameter of the left main bronchus. After the bronchoscopy the child became still more dyspneic, and it was found that the heart had moved from extreme displacement to the right to a position entirely within the left thorax. The breath sounds were still absent on the left, but percussion note was dull, and a roentgenogram confirmed the impression that obstruction was now complete, and a state of massive collapse of the left chest, such as would follow an occlusion of the left main bronchus, had occurred. Ten days later another roentgenogram showed normal expansion of both lungs but a considerable amount of peribronchial infiltration in both. The picture remained of this type for two months more, at the end of which time the child was sent to a sanatorium where she stayed for one year and gained fourteen pounds. At discharge from the sanatorium her roentgenogram showed only minor changes, and now nearly nine years later her parents write us that she is a normal, healthy child without symptoms.

CASE 5.—H. G. (167627), a boy 4 years of age, was admitted to the Children's Hospital in January, 1933, with a chief complaint of coughing for the preceding three months and a vague story of inconstant wheezing in respiration during this time. The family history was negative for tuberculosis, and the child's own history was irrelevant except that he was thought to have swallowed a nail one year previously.

Examination showed rather poor nutrition, a frequent nonparoxysmal cough, diminished breath sounds, but no râles, at the left base. In general, the breath sounds were heard more clearly in the left upper lung than towards the left base, but they seemed everywhere diminished on that side. There was no fever nor important changes in pulse rate or rate of respiration. The reaction to tuberculin was positive to 0.1 mg. of old tuberculin. A roentgenogram of the chest showed: "Diffuse peribronchial infiltration quite generalized on the right. On the left, a distinct fairly dense band extending downward and slightly outward from a point just lateral to the hilus to the extreme base. The area medial to this line is quite dense; lateral to it the lung is emphysematous. Fluoroscopically there was moderate shift of the mediastinum to the left on inspiration. Findings indicate a partial collapse of the left lower lobe and compensatory emphysema of the remaining lung." During the next three weeks, repeated roentgenograms showed these signs to persist to a variable degree. Bronchoscopy was twice done by Dr. Lyman Richards on Jan. 26, 1933, and Feb. 9, 1933; each time the finding was a narrowing of the bronchus to the left lower lobe, seemingly from external pressure; no foreign body could be detected. The child was sent to the State Tuberculosis Sanatorium at North Reading, Mass., and remained there eighteen months, during which time he gained weight and seemed well and had no recurrence of the symptoms. On discharge at the age of 6 years, in 1934, his check roentgenogram was quite negative, as was the case in March, 1942, when he was 13½ years of age.

CASE 6.—W. W. (170405), was admitted to the hospital at the age of 7 years, 9 months, because of exhausting attacks of coughing which had been present for six months. The family history was negative, there was no history of aspiration of a foreign body, and the child had had no fever. During the three weeks immediately preceding admission, there had been an increasing amount of yellow sputum produced. Physical examination showed a rather slender boy in no apparent discomfort. There was good resonance throughout both lungs except for dullness and diminished breath sounds at the right base. No adventitious sounds were heard. The tuberculin reaction was positive to 0.2 mg. of old tuberculin. There was a definite increase in the number of monocytes in the blood smear. Chest roentgenograms showed practically complete atelectasis of what appeared to be the middle lobe on the right with a dense triangular area at the right base medially, and the lung

above this was emphysematous but clear. The left lung was also clear. A bronchoscopy performed by Dr. Lyman Richards showed edematous thickened bronchial walls on both sides. On the medial wall of the right bronchus 2 cm. below the bifurcation was a mass suggesting granulation tissue protruding into the lumen. The bronchus was narrowed below this mass. No foreign body was seen. Part of the mass was removed for biopsy, and sections of it showed material consistent with tuberculous granulation tissue although no tubercle bacilli were found. A presumptive diagnosis of tuberculous mediastinal adenitis was made, and it was assumed that pressure from peribronchial nodes and actual tuberculous infiltration of the bronchial wall and mucosa on the right had caused collapse of the right middle lobe with surrounding compensatory emphysema. The child was sent to a sanatorium and was not seen again until almost two years later. At that time the lung showed slight diminution of breath sounds and resonance at the right cardiohepatic angle. Re-examination of the chest by roentgenogram then showed still a moderate amount of fairly dense infiltration in the lung adjacent to the right cardiac border. At the extreme base laterally just above the diaphragm there was a fairly well circumscribed somewhat mottled patch about 1 cm. in diameter which apparently contained some calcium and had very much the appearance of a tuberculous focus. Except for reaction adjacent to the cardiac border, the middle lobe had become quite well aerated. There were some rather discreet nodules around both hili, but the lungs were otherwise essentially clear.

Seven years later the child was again seen, at the age of 16 years. His history had been quite uneventful during the interim, and a roentgenogram at this time showed no evidence of an active pathologic process and sharply defined areas of calcification at the hili. Physical condition was excellent.

CASE 7.—E. C. (164556), a boy 21 months of age, was admitted to the orthopedic service in December, 1932, because of swelling of the right ankle. The child's tuberculin test was positive, and the complaint was later determined to be a tuberculous process. There was also a hacking cough, the origin of which was not very accurately dated. Films of the chest showed a broad dense band extending along and parallel to the right side of the mediastinum from the apex to the base. This was supposed to be evidence of fluid between the inner margin of the lung and the mediastinum. The right middle lobe appeared to be partially collapsed and quite dense. This was considered evidence of blocking of the bronchus leading to the right middle lobe, particularly since the mediastinum seemed to be somewhat displaced to the right. Physical signs were difficult to evaluate. There was some evidence of the heart being pulled to the right, with percussion note dull on the right posteriorly, and breath sounds much diminished. It was thought probable that a gland, presumably tuberculous, was pressing on and obstructing the bronchus to the right middle lobe. However, review of the history with the parents brought forth evidence of a fit of coughing following choking on a nut some weeks before. Bronchoscopy was done by Dr. Lyman Richards, and a piece of nut, probably almond, was removed from the right main bronchus. This was surrounded by granulation tissue. The whole mass was determined by sectioning to be a portion of nut embedded in tuberculous tissue, since tubercle bacilli were demonstrated in the granulations. The roentgenogram showed considerable expansion of the right lung one month later, though the mediastinum was still shifted. The child died fifteen months later of miliary tuberculosis and tuberculous meningitis.

CASE 8.—D. C. (241055), a baby boy aged 8 months, was admitted to the hospital because of noisy and wheezing respiration since the age of 3 months. During the first weeks of life he had a known exposure to tuberculosis at the hospital in which he was delivered.[8] At 2 months of age his tuberculin test became positive. At 3 months he was noted to have a pronounced wheeze. A roentgenogram of the

chest at 5 months of age showed what was taken to be an enlarged thymus. For three days prior to his entry to the Children's Hospital on April 4, 1940, he had a hacking cough besides the difficult breathing.

Physical examination at this time showed a somewhat obese infant who did not appear ill. One could hear an inspiratory wheeze, particularly during crying. There was slight dullness over the upper part of both lung fields but definite diminution of breath sounds over the left chest. No fine râles were heard, but coarse rhonchi were present over both lung fields. Tuberculin reaction was strongly positive. Guinea pig inoculation of material obtained on gastric lavage was negative for evidence of tubercle bacilli. Roentgenograms showed atelectasis of the left lower lobe with compensatory emphysema of the left upper and some bronchial congestion in the right lung. There were irregular rises in temperature, but these were associated with an otitis media. Bronchoscopy performed by Dr. Carlyle Flake eight days after admission revealed no mass or foreign body in either bronchus, and no definite area of pressure from without was visualized. Nevertheless, the left lower lobe remained collapsed by roentgenogram. A film taken three months later showed the left lung field to be essentially clear. During this three months the physical signs and symptoms had gradually disappeared. Subsequent examination by roentgenogram at nineteen months of age showed some mottling and increased density of the left lower lobe though no atelectasis; there was a small amount of calcification at the left base. At 26 months the chest was clear except for the persistence of a very small calcified residuum in the left lower lobe.

Fig. 1 (Case 9).—Atelectasis of right lower lobe due to exudate and granulation tissue in bronchus.

CASE 9.—M. R. (237379), was transferred to the Medical Ward of the Children's Hospital from the Surgical Ward in December, 1940, at the age of 3½ years. He had previously been on the throat service of the hospital because of tuberculous cervical adenitis, and the tonsils and adenoids had been removed in February, 1940, the latter tissues showing tuberculous foci although no tuberculosis was found in the tonsils. He seemed to be in fair condition at home thereafter, except for two rather brief attacks of what was called "croup." In December, 1940, he was admitted to the surgical ward for excision of an old scar of what appeared to be tuberculous cervical adenitis. However, on the day after admission, roentgenograms

of the chest (which was negative except for slight prominence of the right hilus shadow one year before) showed at this time atelectasis of the right lower lobe and prominence of the right hilus with questionable calcification and a normal-appearing left lung (Fig. 1). Physical examination showed a diminution of

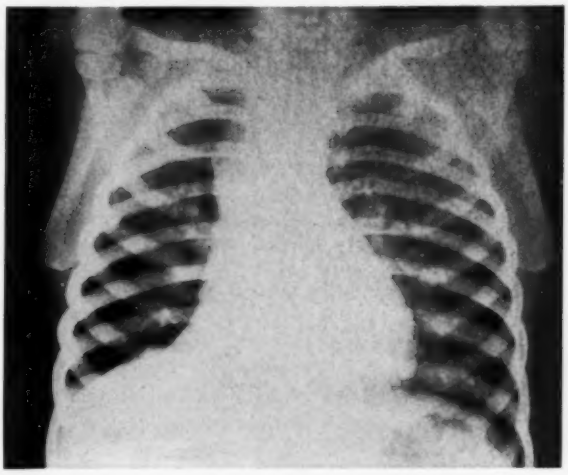

Fig. 2 (Case 9).—Increased atelectasis of right lower lobe.

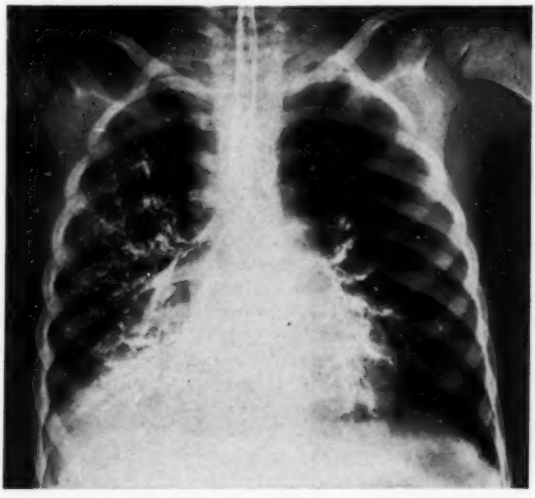

Fig. 3 (Case 9).—Irregularity and narrowing of right lower main bronchus with possible early bronchiectasis in terminal bronchi of atelectatic lobe.

respiratory motion of the right side; the right chest was somewhat dull in back below the eighth vertebra and behind the posterior axillary line. No râles were heard. No changes in breath sounds were noted. The trachea seemed to be in the midline. It was not possible to admit the child to the medical ward until six

weeks later, Feb. 3, 1941, at which time the findings were still much the same (Fig. 2). On the ninth hospital day bronchoscopy performed by Dr. Charles Ferguson revealed a moderate amount of thick yellowish exudate in the right lower bronchus. The exudate was not cultured. About two-thirds of the way down the right main bronchus an area of granulation tissue was seen and was removed by forceps. After this procedure bronchograms were performed with lipiodol. These showed irregularity of the right lower lobe bronchus with slight narrowing of the distal portion of its lumen, and below it a minor degree of what appeared to be early bronchiectasis with the bronchi lying close together in the atelectatic lung (Fig. 3). The granulation tissue which was removed was described by members of the pathology department as showing "hyaline material with scattered lymphocytes surrounded by rings of long, thin fibroblasts. Accompanying the latter are many lymphocytes and plasma cells. Occasional capillaries traverse the section. At the periphery are polymorphonuclear leucocytes, erythrocytes, pyknotic leucocytes, and fibrin. No acid-fast organisms are apparent with tubercle stain." The material thus appeared to be acute inflammatory and granulation tissue but could not be positively identified as tuberculous. The child was transferred to the North Reading State Sanatorium and was still there about one year later. Reports from Dr. Carl C. McCorison, the Superintendent, state that he now has showers of râles at the right base and a triangular area of dullness adjacent to the spine with the base downward. The last x-ray showed questionable calcification in the left hilum and a few flocculent shadows around the right hilum.

CASE 10.—R. L'H. (242146), an 18-month-old boy, was admitted to the hospital on May 8, 1940, because of wheezing for a period of three weeks. There had been prolonged contact with an actively tuberculous mother. Except for the appearance of unproductive cough and associated wheezing three weeks before entry, the past history had been negative. Examination showed a healthy looking infant of good nutrition. The percussion note was slightly more resonant on the right side, but there was a decrease in breath sounds and tactile fremitus over this region. A few transient fine râles were heard at the right base, otherwise the physical findings over the lungs were negative. The liver and spleen were slightly enlarged. The tuberculin reaction was definitely positive. The child was in the hospital about three and one-half weeks, during which time his temperature fluctuated between 98 and 101° F., usually remaining below 100° F. Roentgenograms showed an area of hyperaeration in the portion of the right lung corresponding to the right lower lobe (Fig. 4). The heart and mediastinum were slightly displaced toward the left, and the right diaphragm slightly depressed. Fluoroscopic examination showed a shift of the mediastinum and heart on expiration, confirming the previous impression of obstructive emphysema. The remainder of the lung showed a slight relative increase in the density as compared with the hyperaerated area, but nothing more specific. Further questioning failed to reveal any suggestion that the child had aspirated a foreign body. A bronchoscopy was done by Dr. Carlyle Flake two days after the child's admission, and the findings reported as follows: "The left main bronchus was normal. About 2 cm. from the bifurcation the right main bronchus contained in its anterior wall a granulating mass covered with thick exudate in places and exuding through the center a small amount of purulent material. It had the appearance of a gland which had slowly ruptured into the bronchus. This region was not interfered with in any way, and the patient was returned to the ward in good condition." Since it was thought best not to disturb the area, no tissue was taken for biopsy. Following bronchoscopy, aeration of both lungs seemed to improve by physical examination and roentgenology. The child was discharged to the North Reading State Sanatorium and remained there for about one year at which time a physical examination was negative and his x-ray

showed a small amount of calcification in the right hilum which region seemed a little dense. He was last seen in the Outpatient Department of the Children's Hospital in August, 1941, at the age of 2 years, 8 months, or about fourteen months

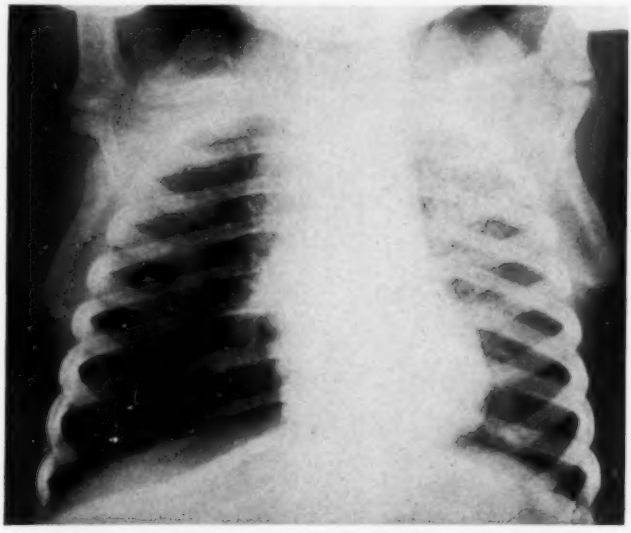

Fig. 4 (Case 10).—Obstructive emphysema of right lower lobe. Granulation tissue was found in right main bronchus.

Fig. 5 (Case 10).—Normal lungs fourteen months after x-ray in Fig. 4.

after his earlier admission. At this time he wns in good condition with a negative chest roentgenogram except for faint questionable calcification in the region of the right hilus (Fig. 5).

CASE 11.—R. L. (257718), a boy, was first seen in the hospital in November, 1941, at the age of 1 year, 9 months. The complaint was of a chronic cough and a slight wheeze in respiration which had begun about six months before, following

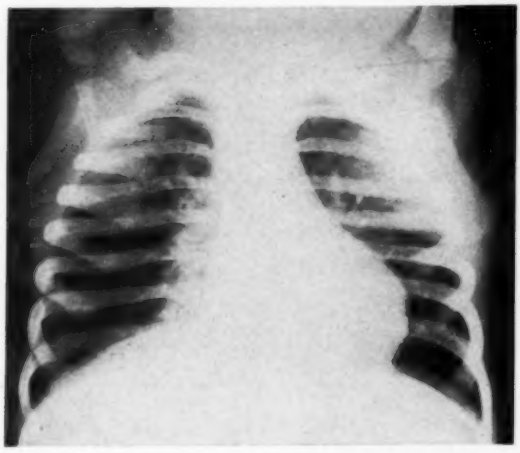

Fig. 6 (Case 11).—Obstructive hyperaeration of left lower lobe.

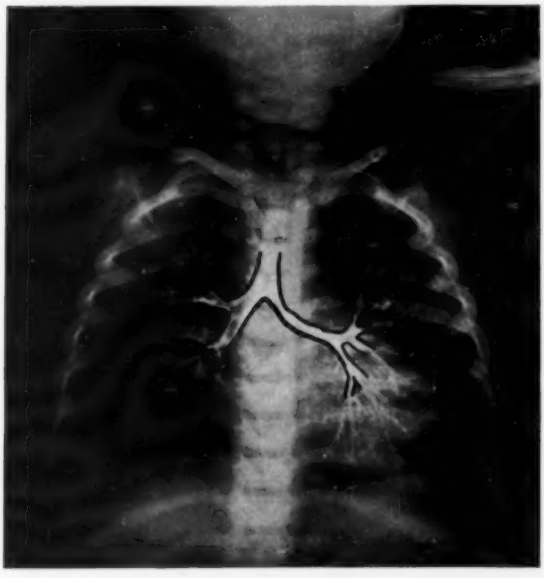

Fig. 7 (Case 11).—Bronchograms showing narrowing of left main bronchus from external pressure. The main bronchi are outlined in black.

an episode of cold and fever. These symptoms had become somewhat worse during the last two months before admission. The child's father had been a patient in a tuberculosis sanatorium several years before.

On physical examination no alteration in percussion or auscultation could be discovered, except for generalized coarse rhonchi. The child was well nourished and had no fever. The tuberculin test with 0.1 mg. of old tuberculin was strongly positive. Roentgenograms showed hyperaeration of the entire left lung and later the left lower lobe in particular, suggesting an obstruction to the left main or

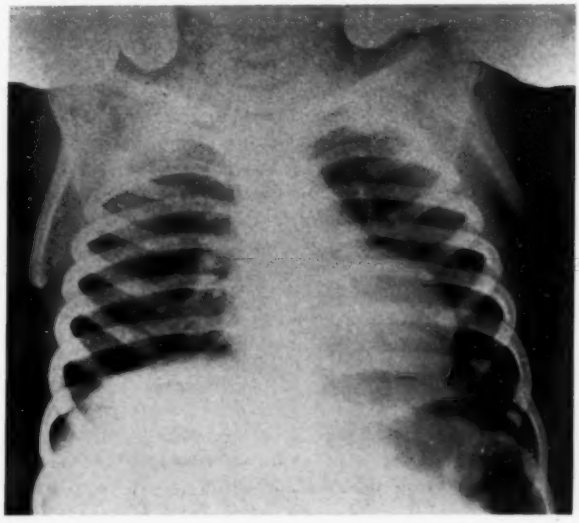

Fig. 8 (Case 11).—Emphysema still present at left base six months after x-ray in Fig. 7.

lower bronchus (Fig. 6). Bronchoscopy performed by Dr. Charles Tucker showed a definite narrowing of the lumen of the left main bronchus which seemed to be extrinsic in origin, and this was confirmed by lipiodol studies showing the left main bronchus to be encroached upon just below the carina (Fig. 7). After five hospital days the child was discharged and has been followed in the outpatient department. A recent x-ray, eight months after the first admission, shows the persistence of some emphysema of the left lower lobe (Fig. 8). No symptoms remain.

Case 12.—V. G. (161506), a girl 3 three years, 9 months of age, was brought to the hospital by her mother who said she had asthma. There was no family history of allergy, and no tuberculosis contact was known. Six months before admission she was said to have had a head cold with a hoarse cough and loud breathing, and five months before admission there was an onset of wheezing respiration which had persisted almost unchanged to admission. There seemed to be no relationship to time of day, activity, or type of food eaten. There was no history of a foreign body being aspirated. Examination showed a well-developed and not acutely ill little girl, whose lungs apparently expanded equally on both sides. On the left side breath sounds were slightly decreased, and whispered voice sounds slightly diminished. Coarse, long expiratory wheezes were heard on this side. Breath sounds were also heard on the right side from time to time, but the picture was a very changeable one as though some intermittent obstruction was being moved about in the bronchial tree. With further study it appeared that the sounds were

more constant on the left side and that most of the variation took place on the right. The tuberculin reaction was positive. Roentgenograms of the chest at admission showed a considerable amount of hazy congestion in both midlung fields, slightly more on the left. The right lung appeared to be hyperaerated and to have displaced the heart slightly to the left. The impression of obstruction to the right main bronchus was confirmed by fluoroscopy within the next two days. Since it was felt that the child might have either a polyp or a tuberculous mass in the right main bronchus, she was examined by bronchoscopy performed by Dr. Lyman Richards one week after her entry, and while the left main bronchus appeared to be normal, an obstruction to the right main bronchus was noted in the form of a small flap or redundant mass of mucous membrane or polypoid tissue which allowed inspiration of air but which closed in a valvelike flap with expiration. The mass was removed from the bronchial wall and on section was found to be tuberculous granulation tissue with acid-fast bacilli in sections stained by Ziehl-Neelsen's method. About three weeks thereafter, a re-examination of the chest by roentgenogram showed still a slight amount of perihilar thickening on both sides of the mediastinum. The lungs were practically equally aerated. The physical signs at this time were not unusual, nor were they abnormal one month after discharge when the child was re-examined, having been at home eating well, gaining weight, and having no fever, cough, or "asthma." The child was again re-examined on April 21, 1942, at the age of 14 years and showed good general health, a negative chest, and on roentgenogram no evident abnormality.

CASE 13.—E. B. (166962), a 7-year-old girl, was admitted to the hospital Oct. 24, 1935, because of inspiratory wheezing of eight weeks' duration. There was a history of some contact with tuberculosis. There was a past history of noisy inspiration at the age of 3 years which lasted for four weeks and terminated abruptly. Otherwise the child had been well until eight weeks before admission when without cough, sputum, or fever she had been bothered by a wheezing noise deep in her chest on inspiration. At first this was intermittent, but after four weeks it became continuous and was heard during her sleep as well as during her waking hours. Physical examination showed good development and nutrition. Both lungs were hyper-resonant, breath sounds normal over the entire right chest, and this side moved better than the left during respiration. On quiet inspiration no breath sounds could be heard over the left chest except at the extreme apex. On forced inspiration, a sudden popping or clicking sound was heard, followed by a loud rasping noise of inspiration lasting until expiration began. Tactile fremitus was markedly diminished on the left. Tuberculin reaction was strongly positive. No tubercle bacilli were found on gastric lavage. Roentgenograms which had been taken one month before admission showed a large irregular calcified lesion in the left hilus, with considerable thickening of the perihilar markings and a dense strand extending out along the medial portion of the right upper lobe, whereas those after admission showed movement of the mediastinum to the right on expiration and left on inspiration, with the whole left lung hyperaerated. It was obvious that an obstruction was partially closing the left main bronchus. The presence of a calcified gland seemed a sufficient reason for these findings. The child was discharged to the Tuberculosis Sanatorium at North Reading and remained there about twenty months, being well and free of symptoms or signs at discharge. Roentgenograms at that time showed "right hilum very dense. Fibrosis in second right front interspace. Some calcification in left hilum and lung markings rather heavy below left clavicle." In the five years since this we have not seen this patient as she has moved to another state.

CASE 14.—R. O. (143761), aged 9 months, was brought to the hospital because of wheezing respiration with intermittent cough which had been present for three months. The cough was not severe, paroxysmal, nor productive. There was no family history of tuberculosis and no history of known aspiration of foreign body. Examination showed a well-nourished male infant whose lungs were somewhat hyperresonant to percussion but who presented diminished breath sounds over the right base, particularly posteriorly. No evidences of bronchial breathing or râles were heard. The tuberculin test was positive. Roentgenograms showed hazy peribronchial infiltration throughout both lung fields, with an emphysematous area at the right base. This condition persisted, and later films showed a dense shadow near the hilus on the right which was considered probably to be due to an enlarged hilus gland. The child seemed to be in no distress and was treated conservatively without bronchoscopy. A third film, taken two months after the first one, showed hyperaeration still present at the right base although the child was gaining weight and the cough had ceased, and physical signs were by this time negative. No further roentgenograms were obtained on this child, and he did not return to the clinic, but a letter from his mother in January, 1935, when he was 5 years old, stated that he was in excellent health and had had no further symptoms.

CASE 15.—G. J. (255485), a colored boy aged 3 years, 10 months, was seen in the outpatient department of the hospital in September, 1941, because of a cough suggesting pertussis and present for about ten days. The father and sister had active pulmonary tuberculosis. Examination showed lungs clear to percussion, with a few coarse rhonchi everywhere audible. A cough plate was not taken, but a blood count was not diagnostic of whooping cough. Ten days later the child returned, his cough having improved, but a wheezing noise having appeared in his respiration. Physical examination showed a well-nourished little boy whose breathing at the moment was quiet. The chest showed no alteration in breath sounds or percussion note. A tuberculin test was positive to 0.1 mg. of old tuberculin, and a roentgenogram of the chest showed considerable enlargement of the mediastinal lymph nodes with a slight amount of hazy congestion surrounding them.

On Oct. 31, 1941, about one month later, the child was again examined, there having been a persistence of occasional wheezing, particularly upon overexertion, during the interval. He had gained 1 pound, 4 ounces in weight. Examination showed loud tubular and almost amphoric breathing in the right chest, particularly in the upper portion, both posteriorly and anteriorly. A few crackling râles were heard in these areas. A roentgenogram at this time showed the enlarged lymph nodes previously reported, considerable peribronchial congestion on the right, and persistent hyperaeration on the left. A shift of the mediastinum to the right on expiration confirmed the probability of an obstructive emphysema on the left, possibly due to the enlarged nodes, although foreign body was considered. The physical findings of increased breath sounds in the right chest were probably a false interpretation of normal breath sounds on that side as compared to diminished sounds on the left side. The mother refused sanatorium care for this child and as he was in no respiratory distress and the diagnosis seemed fairly clear, he was allowed to go home without bronchoscopic examination. During the next month the wheeze and cough disappeared, and on Jan. 8, 1942, two and one-half months after the first findings of hyperaeration on the left, another x-ray showed that the earlier pulmonary disturbances had disappeared. No calcification was visible. The child was well by symptoms and signs, and a last roentgenogram on March 30, five months after the onset of respiratory difficulty, showed no recurrence.

The essential data from these fifteen children have been condensed in Table I. It is obvious by inspection of the table that a rather miscel-

TABLE I

CASE	AGE AT DIAGNOSIS	SYMPTOMS	PHYSICAL SIGNS	ROENTGENOLOGY	BRONCHOSCOPY	COURSE AND REMARKS
1 (D. T.)	1 yr.	Two episodes of wheezing and difficult breathing in five months; some cough	No specific signs	Atelectasis right lower lobe, persisting for six weeks after discovery	None	Normal physical and x-ray findings and disappearance of symptoms; followed twenty months
2 (E. L.)	6 mo.	"Heavy bronchitis," cough, one month	No specific signs	Partial collapse right upper lobe, persisting four months	None	General condition good seven months after onset; roentgen appearance slightly better in last film taken
3 (R. M.)	11 mo.	Wheezing, six months; cough, two weeks	Decreased breath sounds right lung, dullness right apex, hyperresonance right back	Atelectasis (partial) both upper lobes two months before this entry; atelectasis right middle lobe, compensatory emphysema right lower	None	Later course entirely negative during next three and one-half years (tubercle bacilli by gastric lavage)
4 (M. C.)	1 yr.	Variable; increasing cough and some dyspnea during four months	Absent breath sounds entire left lung, with shift of heart to right; later changing to dullness of left lung	Obstructive emphysema left lung, followed by collapse of left lung	Narrowing, left main bronchus	Re-expansion after ten days; good health nine years later
5 (H. G.)	4 yr.	Cough and inconstant wheezing for three months	Diminished breath sounds, left lung, especially at base	Partial collapse left lower lobe; compensatory emphysema rest of lung	Twice showed narrowing of bronchus to left lower lobe	Condition entirely normal nine years later
6 (W. W.)	7 yr.	Paroxysmal coughing, six months; purulent sputum, three weeks	Dullness and diminished breath sounds at right base	Atelectasis of right middle lobe, emphysema in adjacent lung	Granulation tissue in right main bronchus, with narrowing beyond it	Normal findings seven years later except for calcium at both hili

7 (E. C.)	21 mo.	Cough, uncertain duration	Dullness and diminished breath sounds right posterior; heart shifted to right	Partial collapse, right middle lobe	Foreign body (nut) embedded in tuberculous granulation tissue in right main bronchus	Some expansion right lung one month later; died of tuberculous meningitis and miliary tuberculosis fifteen months later
8 (D. C.)	8 mo.	Noisy and wheezing breathing, five months; increased difficulty in breathing for three days	Dullness both upper lobes, diminished breath sounds left lung	Atelectasis left lower; adjacent emphysema; some congestion right upper	No granulation tissue, mass, or narrowing	Gradual disappearance of physical signs and roentgen findings in first three months; calcium in left lower twenty-six months later
9 (M. R.)	3 yr.	Indefinite attacks of "croup"	Diminished respiratory movement right side; dullness right posteriorly	Atelectasis right lower lobe, prominent right hilum (Figs. 1 and 2); bronchograms two months later showed irregularity and slight narrowing right lower bronchus, with atelectatic lung beyond it, and possible early bronchiectasis (Fig. 3)	Exudate and granulation tissue (not positively identified as tuberculous) in right lower and main bronchi	In sanatorium one year later, with some râles at right base and possible calcium in right hilus by x-ray
10 (R. L'H.)	18 mo.	Wheezing and nonproductive cough, three weeks	Slight increase in resonance, right side, with decreased breath sounds and fremitus in this area	(Fig. 4) Hyperaeration, right lower lobe; fluoroscopic confirmation of obstructive emphysema of that area; less marked five days later	Granulation tissue (not biopsied) and exudate, in right main bronchus; appearance of gland which had slowly ruptured into bronchus	Normal fourteen months later (Fig. 5)

TABLE I—CONT'D

CASE	AGE AT DIAGNOSIS	SYMPTOMS	PHYSICAL SIGNS	ROENTGENOLOGY	BRONCHOSCOPY	COURSE AND REMARKS
11 (R. L.)	20 mo.	Cough and slight wheeze for six months	No localizing signs	(Fig. 6) Hyperaeration, left lower lobe; bronchograms show smooth narrowing left main bronchus just below bifurcation (Fig. 7); bronchi otherwise negative; some emphysema eight months later (Fig. 8)	Extrinsic narrowing of lumen of left main bronchus; bronchi normal below this	Symptom free fourteen months after onset
12 (V. G.)	3 yr., 9 mo.	Loud breathing, six months; wheezing, five months	Inconstant; noisy râles on left, with slightly diminished breath sounds; intermittent breath sounds on right	Hyperaeration, entire right lung	Flaplike mass of tuberculous granulation tissue removed from right main bronchus	Normal ten years later
13 (E. B.)	7 yr.	Inspiratory wheezing for two months	On the left, poor respiratory excursion with no breath sounds except suddenly during deep inspiration	Hyperaeration, entire left lung; calcified mass at left hilus	None	No mechanical difficulty in respiration or evidence in roentgenogram twenty months later
14 (R. O.)	9 mo.	Wheezing and intermittent cough, three months	Both lungs hyper-resonant; diminished breath sounds at right base	Emphysema at right base in films two months apart	None	Reported well by family four years later
15 (G. J.)	3 yr., 10 mo.	Cough followed by wheezing for about six weeks	Breath sounds less on left than right side	Hyperaeration of left lung; enlarged hilar lymph node shadows	None	Roentgenograms showed lung fields equal in density two weeks later; general condition good five months after onset

laneous collection of cases is included; nevertheless the association of fairly long-standing obstructive processes with tuberculin sensitivity in young patients makes it seem justifiable to group them together for the following discussion. Moreover, one important aspect of the subject is the variety of mechanisms which have been observed.

The *ages* of these children when the diagnosis was made were, in general, those of infancy and early childhood. Wallgren[9] states that "the more yielding the bronchi, the more easily does compression come into existence. Consequently expiratory stridor is commoner in infants than in older children." Actually nine of these fifteen children were less than 2 years old, a period well known to be characterized by low resistance to tuberculosis.[10] In spite of the combination of three factors: (1) a dangerous age period, (2) an important mechanical disturbance, and (3) a serious type of infection, the outcome seems to have been quite good in the general group of patients.

The *symptoms* presented by these children tended to be of rather indefinite onset and rather loosely described by the parents (and even by the physician) in terms of "heavy breathing," or "noisy breathing," or "wheezing," a word which recurs rather monotonously through the records. Sometimes the onset of symptoms could not be dated by the parents, but in general a period of from three to six weeks or more had gone by before the condition caused the child to be brought to the clinic, so that the manifestations reported were not transient but well-established ones.

The cases have been divided roughly into a first group of nine patients in whom the process had produced atelectasis of some portion of the lungs and a second group of six others in whom the disturbance was an obstructive emphysema. It will be noted that the symptoms were only slightly different in the two groups, although in the patients in Cases 1 through 9 there is perhaps a little more frequent notation of cough, whereas in the patients in Cases 10 through 15, the manifestation was more often simply that of wheezing. It is obvious that such symptoms might be expected from the type of change present since a lesion sufficiently obstructive to cause a complete atelectasis might probably account for a considerable attempt to open the bronchi to air by frequent coughing, whereas an obstruction which allowed the passage of air although only in one direction would not be so apt to have this reflex effect. In one child (Case 4), who suddenly developed a massive collapse of the left lung, there appeared a story of dyspnea of rapid onset, but in only one of the others was the picture marked by an appreciable increase in the effort of respiration, and in this child (Case 1) the difficulty had been minimal.

No special summary of data as to weight and *general physical status* of these fifteen children has been given in the table, but almost all of

them were in surprisingly good physical condition and remained so. Actually the only patients with evidence of malnutrition or other bodily signs of chronic illness were Cases 4, 5, 6, and 7, at least one of whom (Case 7) suffered from an important amount of tuberculosis elsewhere.

Physical signs, as might be expected, depended somewhat on the extent of the lung field which was involved, the persistence of the process, and the number of opportunities for examination. In the nine children whose obstruction particularly resulted in atelectasis, two were repeatedly examined without any changes in physical findings being discovered. These were, however, rather young infants in whom single lobes were involved. In the other patients with atelectasis the expected area of dullness and diminished breath sounds was encountered over the involved region, and sometimes the hyper-resonance of the adjacent lung was notable by percussion. Of the six children with primary emphysema one showed no physical signs except generalized rhonchi. This, too, was a younger patient. The others tended (though not always very strikingly) to exhibit the increase of resonance with associated diminution of breath sounds which would mark the area of air-filled lung whose communication with the trachea had been partially cut off. The examination of the patient in Case 13 was particularly striking; on listening over the involved region in her lung, one could actually hear the airway click open as the bronchus expanded to a point which allowed air to pass the obstruction present. Indeed, this child herself was conscious of the phenomenon and said that at first it kept her awake at night until she got used to it. However, it is probable that many if not most of the patients with obstruction to a portion of the bronchial tree from tuberculous processes must escape the attention of examiners not on the alert for very slight differences in physical signs and not able to combine physical with roentgen diagnosis.

Roentgenograms of the fifteen children were, in general, not difficult of interpretation, although their meaning often became more obvious when considered in the light of the physical findings. It is puzzling that the patient in Case 3, who came to the hospital bringing with him films taken two months before at another institution, appeared to have atelectasis of both upper lobes at that time, but we do not know the physical findings then. Upon his arrival here, the films and physical signs were in fair accord as indicating a collapse of the right *middle* lobe with normal appearing upper lobes and compensatory emphysema of the right lower. In the roentgenograms of another patient (Case 6) it was doubtful whether the collapse involved both the right middle and right lower lobes or only the right middle lobe. Usually there was no difficulty, particularly when fluoroscopy was used, in ascertaining an obvious disturbance of a major airway or in distinguishing between those cases marked by atelectasis and those marked by emphysema, al-

though of course a certain amount of compensatory emphysema was usually present in lung tissue adjacent to that which had become atelectatic.

For various reasons, *bronchoscopic examination* was not done in the patients in Cases 1, 2, 3, 13, 14, and 15. In one instance brochoscopy was missed because the child was left in the hospital only a brief period of time, while in four others this examination was omitted because repeated roentgenograms showed such steady improvement that no instrumental examination was thought necessary. It is our feeling after reviewing this whole set of patients that bronchoscopy should be included in the study of all similar patients in the future. If the services of a skilled bronchoscopist are available, the chances of doing any harm to such children are very slight, while the chances of possible assistance in the way of finding foreign bodies are quite definite. No local abnormality was observed at the bronchoscopy of the child in Case 8, although this child had a very definite story of wheezing and noisy breathing for five months and definite roentgenologic evidence of collapse of the left lower lobe. Disease in that lobe rather than in or near the bronchus may have had something to do with atelectasis, since the calcium discovered roentgenologically in the left lower lobe twenty months later probably marked the region of a primary focus there. Of the other eight patients who were examined by bronchoscopy, three (Cases 4, 5, and 11) showed narrowing or constriction apparently due to pressure from without. In the patient in Case 6 there were both narrowing and the presence of granulation tissue in the bronchus. In three others (Cases 9, 10, and 12) granulation tissue with more or less exudate beyond it was present in the bronchi, while the patient in Case 7 had the interesting finding of a foreign body embedded in tuberculous granulation tissue. Thus, individual and combined lesions of various types were discovered. In passing, it may be noted that no particular form of obstruction was associated with either characteristic type of disturbance in the associated lung or lobe: thus, children whose mechanical difficulty was atelectasis had, in certain cases, narrowing of the bronchus from external pressure, whereas others with the same symptoms and roentgen findings apparently had obstruction of the airway by virtue of granulation tissue within the bronchus itself.

Since no child with a narrowing of the bronchus from external pressure came to autopsy, one can only theorize with regard to gross pathology of the *mechanism causing bronchial constriction.* Spivek[3] shows a drawing indicating how the left main bronchus in one of his autopsy cases was compressed between an enlarged tuberculous gland on either side of it. Hughes and Simpson[1] present a similar picture with the bronchi to the right middle and lower lobe almost completely collapsed by surrounding tuberculous tissue which was probably glandular in origin, and Bilderback and Ashley[7] have shown the same type of specimen. Whether one single peribronchial gland by itself can accom-

plish a complete bronchial occlusion in this manner or whether *all* such occlusions are accomplished entirely by enlarged glands only, and never by fibrocaseous pulmonary infiltration and reparative processes as well, are somewhat academic matters. The fact remains that without a foreign body or increased secretion or occlusion of the lumen by granulation tissue, tuberculous processes adjacent to the bronchi can and sometimes do produce either partial or complete obliteration of the airway.

Granulation tissue removed by biopsy through the bronchoscope in the patients in Cases 7 and 12 was found to contain tubercle bacilli; in the other two biopsies (Cases 6 and 9) the tissue was consistent with that of tuberculosis although the organisms were not discovered. No complete analysis has been made, but the impression is gained from the literature and from our own patients that tuberculous tissue either arising in the wall of the bronchus or penetrating through it by extension from an involved peribronchial lymph node is a slightly more common cause of obstruction than is the pressure effect of an external glandular mass. In our own experience the use of lipiodol has yielded little further information, if any, than was obtained by the bronchoscopic examination. If, however, evidences of coughing have been extreme and one suspects the possible presence or probable development of bronchiectasis, there might be some value in outlining the regions beyond the obstruction by the use of this method. The outcome of our patients has been such as to make us fear this possibility somewhat less than do other observers.

We have been particularly interested in the *prognosis* for such patients because of the general tendency, once the diagnosis is made, to regard the future with considerable gravity. The presence of actual granulation tissue filling or almost filling the inner diameter of a main bronchus is so suggestive of a possible future bronchogenic spread of tuberculosis as to indicate a situation fraught with very great danger. None the less, of these fifteen children only one is known to have died, and in him the cause of death was a tuberculous meningitis which need not necessarily have been brought about by the granulation tissue with its embedded foreign body which was removed from his right bronchus fifteen months before. Of the other fourteen, observed for from four months to ten years (eleven of them for considerably more than one year), all have done extremely well. Late roentgenograms were available in ten. From these and from the available progress notes and examinations, we know of only one possible instance of bronchiectasis and no other chronic lung pathology as developments in any of these fourteen children.

As to *therapy*, there is very little that can be said beyond the simple observation that in this group of small children with no especial therapeutic routine the outcome has been good. In general, as with other tuberculous processes in infancy, the management consists of putting the child in the very best possible physical condition, keeping him from

being freshly infected exogenously and waiting in watchful expectancy until the process has cleared. These patients conform to the general thesis elaborated by one of us,[11] that if the tuberculous infant is alive within twelve to eighteen months after diagnosis, the likelihood of a fatal termination thereafter is almost nil, unless this occurs during or after adolescence.

SUMMARY AND CONCLUSIONS

The case histories of fifteen infants and children in whom tuberculosis was the cause of mechanical obstruction to the bronchial passages have been presented and discussed. The following conclusions have been drawn from our experience with these patients:

1. Tuberculous processes may produce either atelectasis or emphysema, depending upon the completeness with which air passages are obstructed. Either of these conditions may succeed the other in the same child.

2. Evidences of obstruction may be the only noticeable symptoms or signs. The general physical status often remains good.

3. Younger children and infants present such conditions more often than do older ones.

4. Bronchoscopic examination is a recommended diagnostic procedure since it determines whether the obstruction is produced by extraneous pressure or intrabronchial granulation tissue. Moreover, in one patient a foreign body embedded in tuberculous tissue was found and removed by this method.

5. No other specific mode of therapy is recommended, and treatment need only be the general hygienic care of the tuberculous child.

6. Although collapse or emphysema may remain for six months or more, the ultimate outcome has been one of complete recovery in the large majority of these patients.

7. Long-standing collapse of a lobe due to complete bronchial obstruction led to evidence of questionable bronchiectasis in only one of seven children who could be followed after such a process.

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EARLY OPERATION IN PREMATURE CRANIAL SYNOSTOSIS FOR THE PREVENTION OF BLINDNESS AND OTHER SEQUELAE

Five Case Reports With Follow-Up

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PREMATURE synostosis of the cranial sutures has sequelae in a high proportion of cases, which, in our opinion, are serious enough to justify reasonable attempts at prevention. So far as we are aware, however, no reports have been published to show that early, preventive measures are actually feasible and useful other than our paper of 1927.[1] Several writers[2a-f] have described operative procedures carried out later, after sequelae had become advanced and damage, largely irreparable, had been done. This is particularly unfortunate since the disorder can nearly always be recognized at or soon after birth, and, as will be shown, the optimal time for preventive operation is during the first few months of life.

The commonest and, for purposes of the present discussion, the most important cranial synostoses fall into three main groups.[3] The first and probably most common involves closure of the whole or part of the sagittal suture with narrowing of the skull in the parietal region, compensatory lengthening of the skull in its anteroposterior dimension, particularly in the occiput, and often widening and elevation of the frontal region (scaphocephaly). The second involves the coronal sutures; here normal growth in the anteroposterior dimension is prevented, the skull becomes short, broad (brachycephaly), and often high in the posterior parietal region. The third, which is the most dangerous, involves one or both of the coronal sutures and the sagittal suture and prevents normal expansion both in the transverse and anteroposterior directions; the skull can then expand only in the vertical direction and becomes high and tower shaped (acrocephaly, oxycephaly, turricephaly). The brain itself, in all these conditions, is primarily normal.

Deformity of the skull is a resultant of two factors: limitation of expansion in directions perpendicular to the line or lines of sutural closure and overexpansion from growth pressure of the brain acting on regions where sutures remain open. The deformity is always conspicuous and frequently very bizarre. Later on, compensatory expansion along free suture lines in many cases becomes inadequate and cerebral growth then causes progressively increasing intracranial pressure which in severe cases may reach levels as high as 500 mm. of water.[4]

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Under such conditions, the inner table of the skull is thinned—convolutional atrophy as seen by x-ray is extreme—and in some cases reaches the point of penetration, with spontaneous herniation of the brain; the orbital plates are depressed, resulting in exophthalmos which is sometimes extreme (lagophthalmos) and may lead to corneal ulceration; the ventricles are narrowed; and, in a high proportion of cases, papilledema with later secondary atrophy ensues. The symptomatic effects of the chronic increased intracranial pressure are headaches, vomiting, failing vision, convulsive seizures, and mental deterioration, all of which are common. In Günther's[4] tabulation of seventy-four cases of oxycephaly from the literature, sixty-seven (or 91%) of the patients developed optic atrophy. Disturbances of the first and eighth nerves have also been reported. Similar effects from closures of the sagittal suture[4, 5a, 5b] alone and of the coronal sutures alone, while less common than when both are closed, have been reported, but no separate statistics on these are available. Finally, it should be mentioned that in all patients the deformity itself is so marked as to constitute a cosmetic handicap of considerable importance.

TABLE I

OCULAR DISTURBANCES IN OXYCEPHALY

	NUMBER	PER CENT OF TOTAL
Optic atrophy	67	92
Amaurosis	45*	76*
Exophthalmos	55	74
Divergent strabismus	46*	78*
Nystagmus	51	68
Total number of cases	74 (59*)	

Condensed from Günther's[4] compilation of five series of case reports.
*In one series of fifteen cases included in the compilation, the details starred were not noted.

The possible value of linear craniectomy in preventing the sequelae of premature synostosis was mentioned by Jacobi[6] in 1894, by Mehner[7] in 1921, and by one of us[8]—unaware at that time of earlier suggestions—in 1924. In the last of these, it was stated that the optimal age for the operation was at or before 6 months. The reason for so early an operation is seen in the graphs of cerebral growth (Figs. 1 and 2). The weight, which may be taken as corresponding closely with the volume, of the brain doubles in a little more than the first seven months of postnatal life and trebles in about two and one-half years. At first, the very rapid early growth is usually well accommodated in the presence of synostosis by compensatory overexpansion along the lines of open sutures but at the expense of increasing deformity. By the end of the first year, however, and increasingly during the next two years, as the cranium becomes thicker and denser and as the remaining sutures become denticulated and interdigitated, compensatory expansion becomes inadequate to prevent increase in intracranial pressure. Papill-

edema, optic atrophy, and failing vision are rarely seen during the first year but usually appear between then and the end of the third year, occasionally as late as the sixth.[4, 9] Hence, in order to reduce deformity as much as possible, we believe operation should be done before the age

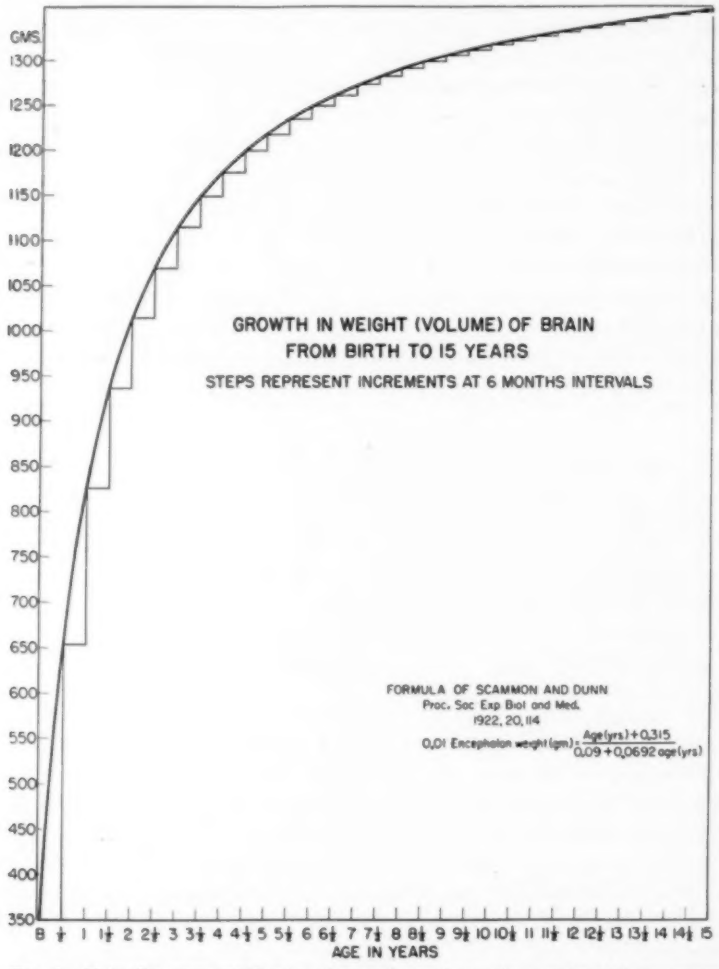

Fig. 1.—Note the very rapid rate of growth in the early months and its progressive decline with advancing age. The formula was based on 2,956 observations with an average percentage deviation of 1.75 per cent of the calculated from the observed values.

of 6 months and, to prevent loss of vision, before the age of 1 year. At present, we suggest 1 to 3 months as the optimal age when operative risks are reasonably low and the prospects of satisfactory results are best.

SURGICAL PROCEDURE

The surgical procedure has been modified somewhat with increasing experience, particularly in respect to increased width of excision, its extension well into the sutures with which it connects, and, in the case of sagittal synostosis (scaphocephaly), to excising two strips rather than one. The operation which is now suggested is as follows. For closure of the sagittal sutures, strips of bone approximately 2 cm. wide should be removed from the parietal bones on either side of the sagittal

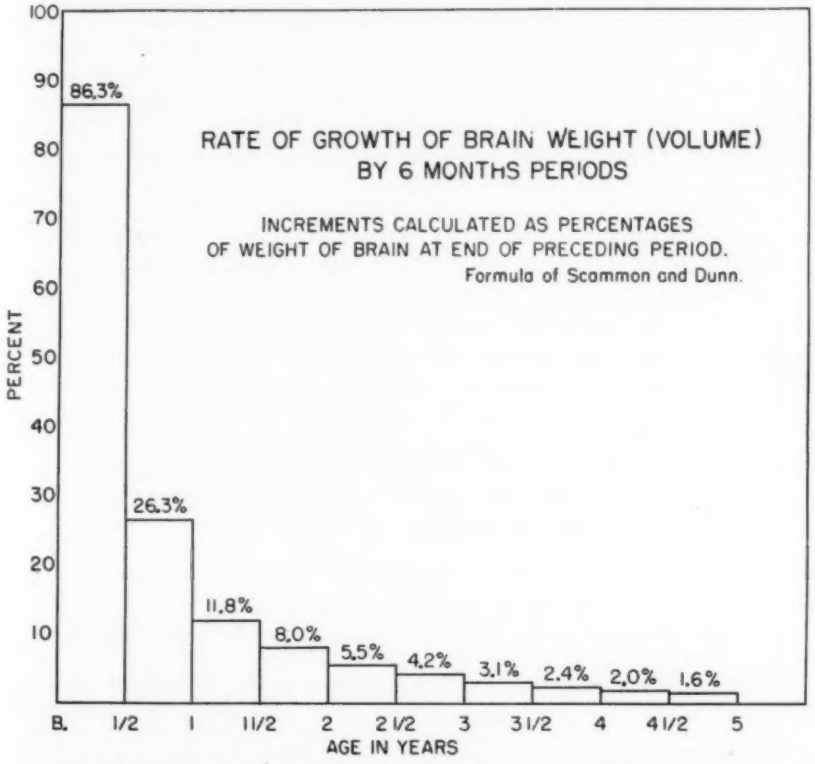

Fig. 2.—Calculated from the same formula as Fig. 1, the graph brings out sharply the relatively very great increase in brain size during the first six months and, by inference, the desirability of correcting the constrictive malformation of the skull during this period.

suture far enough from the midline to avoid danger of injury to the longitudinal sinus and emissary veins. Bone needs to be removed over the longitudinal sinus only at a point just anterior to the lambdoid suture, so that there will be a connection between the two defects in the parietal bones. After this procedure it will be found that the anterior portion of the parietal bones can be sprung apart more easily than the posterior portion, because the lambdoid suture anchors the posterior

end, and the anterior end is free at the anterior fontanel. It might, therefore, be better to cut channels in the posterior portion of the parietal bones, parallel to the lambdoidal suture, for a distance of two or three inches; this has not, however, been done in any of our cases with the exception of J. F.

For closure of the coronal sutures, excision of a strip of bone 2 cm. wide is made just posterior to each of the closed sutures, extending downward from the anterior fontanel to the squamous portion of the temporal bones. When both coronals and the sagittal suture are closed, transverse and longitudinal excisions are made.

Before operation, a cannula should be tied into a vein of the foot or lower leg; through this, 5 per cent glucose solution is run slowly during the operation, and later a transfusion of whole blood is usually given before the patient leaves the operating room.

No fatalities or serious postoperative complications or sequelae have occurred in our experience.

The first operation was performed by one of us (E. B. T.) in June, 1924, on our patient J. A. C. and was reported by us in 1927.[1] This patient has been followed up to April, 1942, and his completed history will be given presently. Four other case reports are added.* Two other cases in our records, in which late operation was done, are not included. The number of patients available to us at the early period which we regard as desirable for evaluating the benefits of the proposed procedure has been small, and in one of our patients insufficient time has elapsed to permit appraisal of more than the immediate results. It will be noted that in two of our cases (N. M. and V. G.) operation was performed at the age of a little over 8 months, or somewhat later than what we regard as the optimal age.

CASE REPORTS

CASE 1.—J. A. C., a white American boy, was born Dec. 12, 1923, and was admitted to Stanford University Hospital Jan. 12, 1924, because of deformity of the head. The only symptoms were constant crying and frequent vomiting.

The head was elongated and narrow in the parietal region. The anterior fontanel was triangular, its posterior border a straight transverse line; the metopic and coronal sutures were open. The line of the sagittal suture was firm on pressure and elevated, forming a ridge from the anterior to the posterior fontanel. The occipital region was prominent and apparently elongated. No syndactylism or other bony abnormalities were found. On crying, the veins of the scalp became much engorged.

X-ray confirmed the clinical impression that the sagittal suture was synostosed and that the other main cranial sutures were open.

On readmission April 17, 1924, the folowing notes were made: The face was symmetrical, but the right side of the forehead was somewhat more prominent than the left. The right parietal bone was higher and more rounded than the left. No exophthalmos was present. The profile of the skull rose sharply to a high point just behind the fontanel and back of this slanted downward and backward. The apparent projection of the occiput was somewhat less than before. The left parietal region

*One case report was kindly supplied by Dr. Frederick A. Fender and one by Dr. Frederick L. Reichert, who performed the operations.

was flattened. There were several very prominent veins over the parietal and frontal regions. From above, a marked frontal asymmetry was seen, the right side projecting. The anterior fontanel was now very narrow, about one-fourth of an inch wide and 1¼ inches long; the anterior angle was acute and ended about two inches above the glabella (open metopic suture). The left angle could be felt, but the left coronal could not be followed by palpation. The right angle was felt about one-half of an inch posterior to the left, and the right coronal could be followed downwards about one-half of an inch. The impression was obtained that the left coronal suture was closed and that the right coronal was closing.

The next admittance was on June 18, 1924, when the baby was 6 months old. At this time palpation gave the impression that both coronals and the sagittal were closed. The fontanel could not be felt. Both eyes showed moderate proptosis. The fundi were normal.

In the x-ray of June 18, the coronal sutures could not be identified and appeared closed, although the bone in the regions where they are normally seen looked thinner than the adjoining bone. The fontanel appeared to be covered by bone and was distinctly elevated. The sagittal suture was definitely closed.

Operation was performed by one of us (E. B. T.) on June 19, 1924. A transverse incision was made from one squamoparietal suture to the other. The scalp was turned back to the juncture of the sagittal and the lambdoid sutures. The periosteum was raised along the suture lines. The lambdoid suture appeared normal; the sagittal appeared to be completely closed, as did the upper portion of the right coronal. The left coronal was thought to be open, though narrow. The fontanel was to the left of the midline; running from its anterior end was an open suture (metopic). Craniectomy 1 cm. wide was done from the lambdoidal to the coronal just to the right of the midline and from one squamoparietal to the other.

The baby made an uneventful recovery from the operation and was dismissed on June 26. The child was followed in the Stanford Children's Clinic and Hospital and in our own offices.

July 8, 1924. The shape of the head had improved and the eyes were slightly less prominent.

Aug. 12, 1924. The shape of the head had changed and was now quite symmetrical except that the right frontal region was still prominent. The sagittal suture was now wide, 1.5 to 2.0 cm., resembling a fontanel. The baby was definitely brighter and more active. The eyes were less prominent. The temporal regions were less prominent. The veins of the scalp were no longer distended. The mother reported that the baby was crying much less. X-ray showed that the coronal cuts were nearly twice as wide as just after operation, and the sagittal incision had increased about 3 mm.

Oct. 21, 1924. The baby was walking without aid and speaking a few words. The head circumference was 47.8 cm. X-ray showed that the channels were beginning to fill with new bone. The coronal cuts, however, were still wider, by 2 to 3 mm., than they had been in August. The sagittal cut was about the same width.

April 9, 1925. A thin layer of new bone had filled the channels but these were clearly visible in the x-ray. The coronal channel was a little narrower than in October. There was a slight elevation at the vertex over the sagittal channel.

April 25, 1925. The head appeared normal in shape. There was no proptosis. The child appeared bright.

July 2, 1925. There was slight bulging of the temporal fossae and slight flattening of parietal region superiorly. The child, who was now 19 months old, talked freely, forming short sentences, repeating part of the alphabet and numerals from 1 to 10.

Nov. 26, 1926 (2 years, 11½ months of age). He could say the complete alphabet and spell five three-letter words. The craniectomy was closed, but the transverse cut could be traced as a shallow depression. The cranium was rounded and not

Fig. 3.—*(Legend on opposite page.)*

misshaped, the asymmetry being barely noticeable. The postparietal region was very slightly flat, and the prominence over the ears was less marked.

July 12, 1927. The condition of the head was about the same. No ocular complaints were obtained. Intelligence appeared to be excellent. X-rays showed an increase in convolutional markings throughout. The sella appeared normal. The areas of excision, covered with thin bone, were still visible.

April 16, 1928. X-ray showed growth of nearly a centimeter since last July, 1927, in the sagittal and coronal planes. The convolutional markings remained overly prominent. An area, about one inch wide, of thin bone in the site of the sagittal channel was more plainly visible than in the film of July 12, 1927; in it the lines of the inner and outer tables were thin, irregular, and slightly elevated over the vertex, suggesting a pressure effect.

Dec. 26, 1928. The boy, 5 years old at this time, appeared bright and was beginning to read. A rough visual test appeared normal. He had been blinking and having some lacrimation lately. There had been no headaches.

July 13, 1929. The convolutional markings were a little less prominent than before. The thin area previously noted was somewhat denser and less elevated.

Dec. 22, 1930. He was in high second grade and had been recommended for promotion. He was said to be good at arithmetic, handwriting, and memory. There had been no headaches or visual troubles. There was no proptosis.

March 22, 1932. He had had no headaches or other complaints and no visual trouble. He was in the high fourth grade. The shape of the head was about the same. There was no proptosis, but there was slight bulging of the temporal region just above the ears.

Dec. 29, 1933. He was said to squint when reading and to hold the book near to his eyes. Pupils and fundi were normal. Examination after homatropine showed no notable abnormalities.

Oct. 1, 1934. He was admitted to Stanford University Hospital for observation. He had been having a number of "dizzy spells" for the last few months accompanied by a sensation of being "high up in the air." There had been no nausea, vomiting, headache, ataxia, staggering, or falling. The physical examination, including a careful neurologic test, was negative. Special examinations of hearing (audiometer) and of vestibular function were negative. The special eye examination showed normal fields; visual acuity, R. 15/15; L. 15/20; good convergence; normal fundi; normal pupillary reactions. X-ray showed considerable increase over the last films in all diameters of the skull; the convolutional markings were less prominent than before. There was no erosion of the clinoids. The thin area previously noted was still visible but still denser than before; the inner and outer tables appeared more regular at this place. No explanation for the dizzy spells was found.

Nov. 10, 1934. There had been no further dizzy spells; no headaches.

May 25, 1935. There were no complaints; no headaches or dizziness. He was now in the eighth grade.

July 5, 1935. Special psychometric tests showed a mental age of 15 years, 8 months; calendar age, 11 years, 7 months; I.Q., 135 (superior intelligence).

Visits on Aug. 14, 1936, July 24, 1937, and Jan. 10, 1938, were made for incidental disorders, unrelated to the cranial disturbance.

Fig. 3.—Case 1 (J. A. C.). *A*, Jan. 14, 1924, at age of 5 weeks. The skull has the typical scaphocephalic elongation with flattening over the parietal region. The coronal and lambdoid sutures are visible. The bone over the sagittal suture appears dense and somewhat elevated, corresponding with the palpable ridge.

B, June 18, 1924 (one day before operation), at age of 6 months. The coronals cannot be distinctly seen; the fontanel appears to be covered by bone which is noticeably elevated.

C, Aug. 12, 1924, eight weeks after operation. The coronal channel shows some new bone formation below but is wider than just after operation. Note the well-rounded profile in the parietal region.

May 20, 1938. He was now 14½ years old and a "high sophomore" in high school. He had had no headaches or visual troubles. The head was not conspicuously abnormal. X-rays on May 24 showed no perceptible growth since the last examination. The thin area to the right of the midline in the sagittal plane was still visible.

Fig. 4.—Case 1 (J. A. C.). May 24, 1938, at age of 14½ years. There is no notable abnormality in appearance.

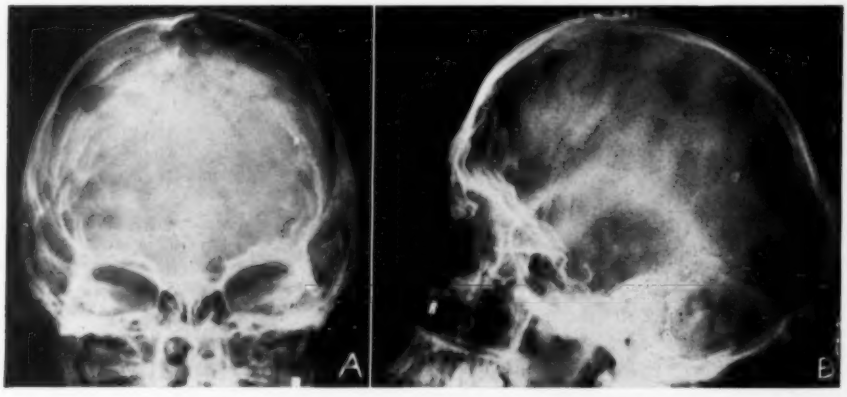

Fig. 5.—Case 1 (J. A. C.). Jan. 21, 1941, at age of 17 years, 1 month, sixteen years, seven months after operation. *A*, Anterior view; *B*, lateral view. The skull is thicker and the convolutional markings much less than before. The thin area at the right of the midline is still present, but the overlying bone is somewhat thicker than previously. The head is moderately brachycephalic.

Jan. 21, 1941. The boy was tall, healthy, and vigorous. The eyes appeared a little far apart, but there was no proptosis. The calvarium appeared slightly high, and the skull was moderately brachycephalic. He had had no visual disturbances and no headaches. The fundi were perfectly normal. He was doing well in high school and expected to go to college the next fall. The x-ray appearance of the skull was practically unchanged. The thin area was still visible.

A letter from his mother written in April, 1942, reported no complaints related to the head. A photograph taken in June, 1940, showed a young man of good appearance. He was 18 years, 6 months of age.

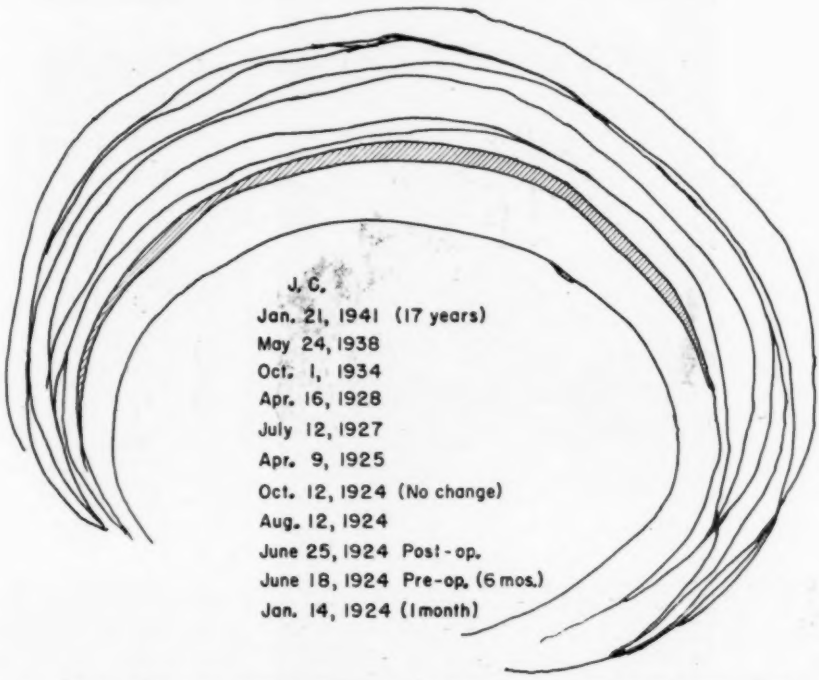

Fig. 6.—Case 1 (J. A. C.). Tracings from lateral x-ray views of the skull. The shaded area shows the expansion of the skull that occurred within six days after operation. Later expansion and growth of the cranium appear to have been normal throughout in the vertical and anteroposterior planes though relatively somewhat greater in the former. The fixed point in this and the other tracings is the sella turcica.

Case 2.—V. G., a white female, was born Aug. 20, 1930, and was first seen at the Stanford Children's Clinic May 7, 1931, where she had been sent because of malformation of the head. She had been deserted by her parents, and a complete history was unavailable. The malformation had been noted at least as early as 3 months and had become more marked. No complaints referable to the deformity were elicited. She seemed to be bright, alert. The head was notably shortened in its anteroposterior diameter, increased in its vertical and lateral dimensions. Its circumference was 39.5 cm. The anterior fontanel could not be felt. No other bony malformations were found. The eyes were normal in all respects, including the fundi.

X-ray showed no trace of the coronal sutures. The sagittal and lambdoid sutures were normally open. There were several wormian bones in the lambdoid.

Operation was performed by Dr. Frederick L. Reichert on May 12, 1931, when the baby was 8 months, 3 weeks of age. A strip of bone about 1.5 cm. wide was removed along the line of the coronal sutures, and, in addition, a linear incision was made with the Gigli saw about 3 cm. posteriorly, on each side, from the lower ends of the excised strips.

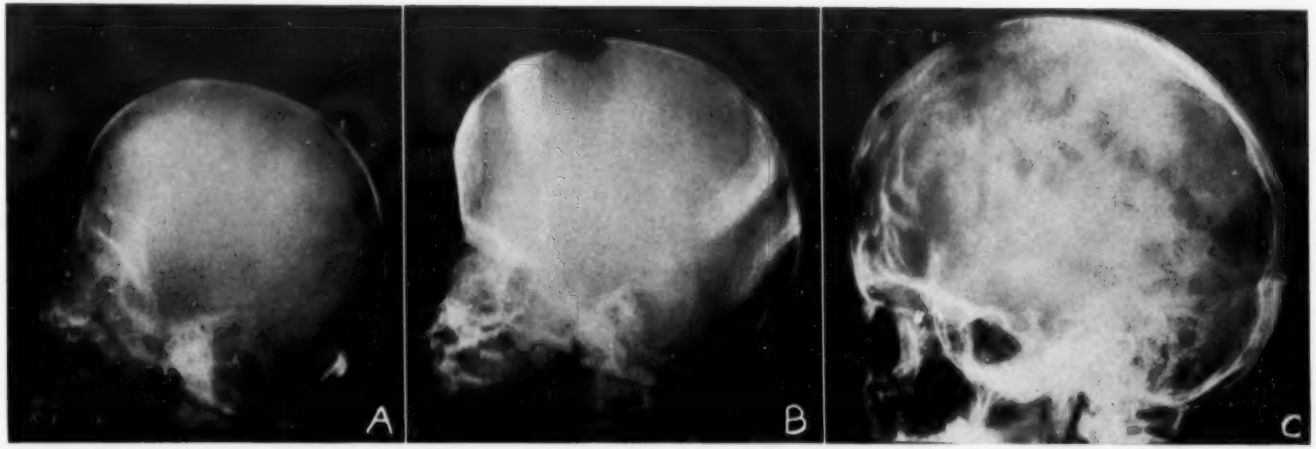

Fig. 7.—Case 2 (V. G.). *A*, May 8, 1931, at age of 8½ months, four days before operation. No trace of the coronal sutures can be seen. There is marked brachycephaly and increase in vertical dimensions of the skull.

B, Oct. 9, 1931, five months after operation. (The immediate postoperative films were unsatisfactory for reproduction.) The coronal channels are wide open above and broader than just after operation, but there is considerable remineralization below. The profile shows both longitudinal and vertical expansion.

C, April 17, 1942, at age of 11 years, 8 months, eleven years after operation. Convolutional markings, first noted Sept. 10, 1934, are still present, but the skull is generally thicker than in the previous film. The "safety-valve" opening remains open after eleven years, both tables lacking continuity. Tracings show continued expansion, somewhat more in the longitudinal than in the vertical direction, but the profile is still that of brachycephaly.

An x-ray on May 18, taken from above, showed the excision to be about 1 cm. in width.

The postoperative course was satisfactory. The child was dismissed on May 23 in good condition.

She returned on Oct. 9, 1931, when an improvement in the profile was noted. X-ray showed the channel to be wide open at the vertex and beginning to fill in below; its width was about 50 per cent greater than it had been in May. On Jan. 21, 1932, some further improvement was noted. The gap, still open at the vertex and about 3 mm. wider than in October, had filled in with new bone in its lower half.

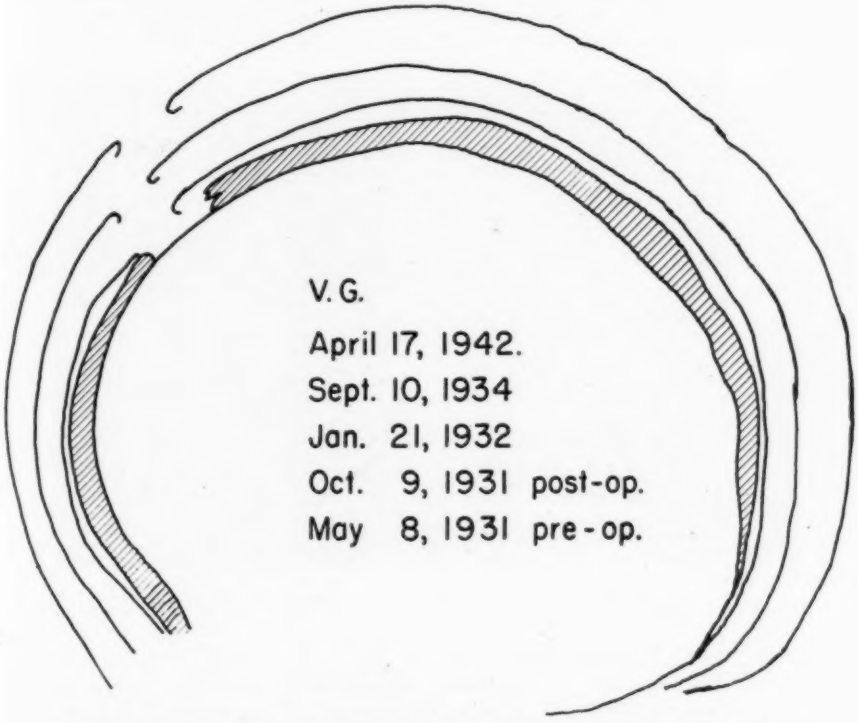

Fig. 8.—Case 2 (V. G.). Profile tracings from x-rays. The shaded area represents the growth five months after operation. It will be noted that the skull has grown well in both longitudinal and vertical directions. The operative gap at the vertex appears to be of about the same width in 1942 as it was in 1931.

She was next seen on Sept. 10, 1934, when she was 4 years old. No clinical note was made, but an x-ray was taken which showed that the skull was still somewhat oxycephalic in appearance but much less so than before, and the increase in cranial capacity was considerable. The channel of bone was still open through both tables at the vertex and extended downward about 1 cm. as measured on the lateral projection; below this, the bone looked slightly thin. A trace of convolutional marking was visible in the frontal region.

The patient was not seen again until April 17, 1942, when she was 11 years, 8 months old, almost eleven years after her operation. She was a bright, responsive

child of rather pleasing appearance. Her school record was consistently of "S" grade (the highest given), and she was one of the youngest members of her class, the high sixth. She had occasional headaches, but these were said to have been brief and related to eyestrain, usually movies. The head looked somewhat high and short anteroposteriorly, with a maximum length of 16.6 cm. and lateral diameter of 13.7 cm., giving a cephalic index of 0.83. The corresponding measurements on May 7, 1931, just before operation, had been 12.0 cm. and 12.5 cm., with an index of 0.96. The head had therefore changed in proportions in the direction of greater length and marked lessening of its brachycephaly. Vision was 10/10 in both eyes, and the fundi were entirely normal. X-ray showed the channel at the vertex to be still open, both inner and outer tables lacking continuity, and perhaps a little wider than in 1934; below this, the bone was perceptibly thin. Convolutional markings were visible in the frontal region but of only moderate degree.

Fig. 3.—Case 2 (V. G.). April 18, 1942. The head is brachycephalic and high vaulted. The appearance is not, however, seriously abnormal. There is no proptosis.

CASE 3.—F. H., a white male, was born Jan. 25, 1938, weighing 8 pounds, 10 ounces. Malformation of the head was noted very early. A snapshot taken at one month shows scaphocephalic deformity with flattened parietal regions and a midline longitudinal ridge at the vertex. He was seen first by us on April 6, 1938, at the age of 2½ months.

At or soon after birth the mother noted that the head came to a peak at the back; there was a ridge in the midline, the forehead was high, and the head was narrow posteriorly. When first seen by us early in April, these descriptions were confirmed. The anterior fontanel was open, being long and narrow (11 × 3 cm.), and the lambdoidal and coronal sutures apparently were open, but the sagittal suture was closed and its place taken by a ridge. The frontal region was raised, and the eyes were possibly a little protuberant, the sclerae showing above the pupils. X-ray showed closure of the sagittal suture. The line of the suture had become denser since March 21, the time of the first picture. Operation was advised and was performed by one of us (E. B. T.) on April 20, 1938, when the boy

was 12 weeks old. A strip of bone 8-10 mm. wide was excised to the left of midline from the anterior fontanel into the lambdoid.

The postoperative course was marked by the occurrence of considerable anemia which responded promptly to transfusion and did not have to be repeated. Nine days after operation x-rays showed that the excised area had widened from the original width of 8 to 10 mm. to 18 mm.

On May 27, five weeks after operation, the increased width of the parietal region and the improved appearance of the head in general were obvious. X-ray showed that the channel had further widened to 22 mm.; its edges were sharp, and there was no apparent new bone formation. On August 19, four months after operation, the excised area appeared on palpation to be filling in with new bone; the head was of normal width and height; it was symmetrical and well shaped; the scaphocephalic appearance had virtually disappeared; there was no proptosis.

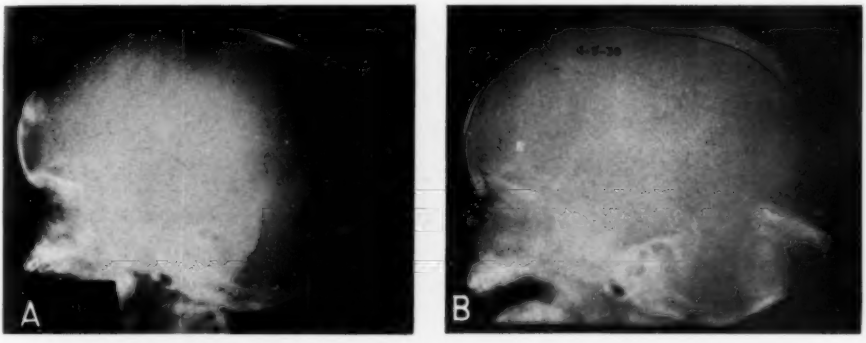

Fig. 10.—Case 3 (F. H.). *A*, April 5, 1938, at age of 10 weeks, two weeks before operation. The closed, ridged sagittal suture shows as an elevated, dense line. The postparietal region is flattened and the occiput prominent.

B, April 26, 1938, six days after operation. The expansion of the skull as shown by the superimposed tracing from the preoperative film is so marked as to suggest that some increase in intracranial pressure had been present.

X-ray on Feb. 20, 1939 (frontal exposure), showed that the outer table had reformed in front, but the inner table showed an interruption about 17 mm. in width. On April 24, 1940, the channel in the inner table was seen to be about 1 cm. broad anteriorly and about 3.5 cm. wide in its midportion. There were no convolutional markings. On Jan. 22, 1941, the channel was about 7 mm. wide anteriorly and 3.5 cm. wide posteriorly, consisting of an area of thin bone. On Feb. 2, 1942, the thinned area was barely visible in front but more clearly so posteriorly. The head had grown symmetrically and surprisingly in volume; however, there were no convolutional markings in its anterior two-thirds and only moderate ones in the occipital region. The sella and clinoids were normal.

No headaches have been noted at any time. The vision is excellent and the fundi, on repeated examination, have always been perfectly normal. The parents report that a recent psychometric examination at Palo Alto showed advanced intelligence. Physical examination at the last visit in February showed the head to be rather long with a broad, high forehead and slight flattening of the parietal regions. There were no prominent scalp veins and no proptosis. The child is notably good looking. The only palpable trace of the craniotomy is near the lambdoid suture where a slight indentation can be made out.

Case 4.—N. L. M., a white male, was born Jan. 23, 1939, and was first brought to the Stanford Children's Clinic Aug. 16, 1939, for malformation of the head

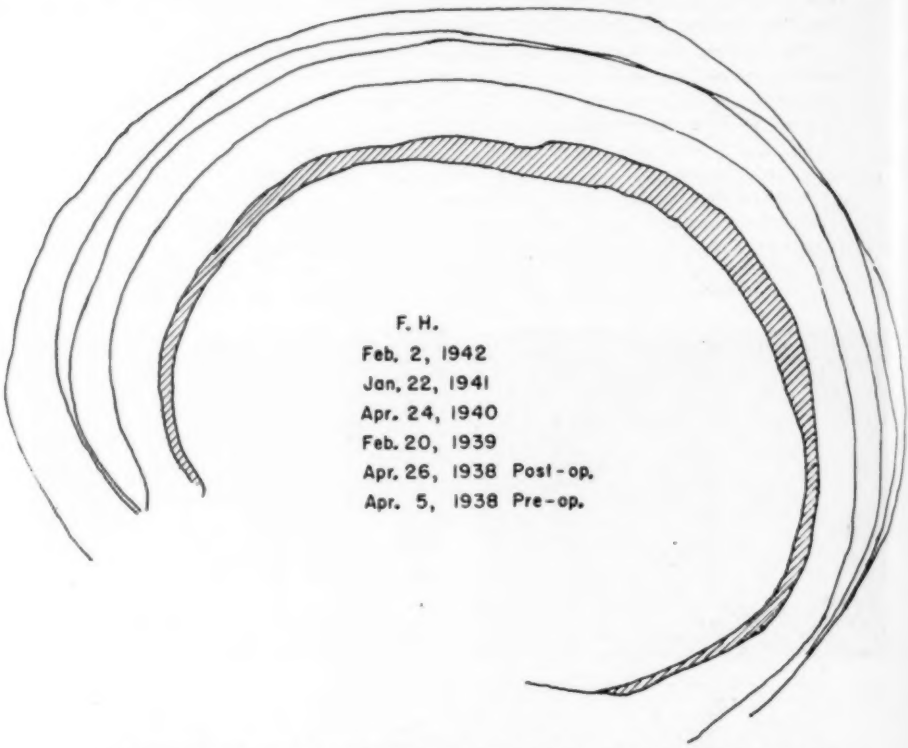

Fig. 11.—Case 3 (F. H.). Superimposed tracings from the x-rays. The remarkable expansion of the skull both immediately after operation and during the following period of almost four years strongly suggests that without operation pressure sequelae might have occurred. There has been no clinical or other evidence of hydrocephalus at any time or of increased intracranial pressure since operation.

Fig. 12.—Case 3 (F. H.). Feb. 2, 1942, at age of 4 years. The appearance is not abnormal. There is no proptosis.

Fig. 13.—Case 4 (N. L. M.). *A*, Oct. 2, 1939, at age of 8 months, 10 days, seven days before operation. The skull is scaphocephalic with closed sagittal suture, which is seen as a dense thick strip running from a point just behind the anterior fontanel to the lambdoid. The coronal sutures are visible a short distance below the fontanel as two narrow lines. The fontanel is capped with bone.

B, Jan. 3, 1942, two years three months after operation at age of 3 years. The coronal cut is still completely open over a small area at the top, and below it the old channel is represented by an area of thin bone considerably wider than the original cut. A trace of convolutional marking is seen in the postparietal and occipital regions but no more than is seen in many normal skulls.

C, Oct. 11, 1939, two days after operation. The coronal cuts are well outlined, but the sagittal cut, which was a little wider than the coronal, is detectable only by the absence of the profile strip of density which was seen in the preoperative picture.

which had been noted at birth ("head shaped like an egg"). He was admitted to Stanford University Hospital Oct. 2, 1939. The cranium was elongated with a marked elevation of the frontal region. The anterior fontanel, palpable in August, was no longer so in October. The occipitofrontal circumference was 48.5 cm. The cephalic index (from the x-rays) was 0.71. The child in other respects, including intelligence and behavior, appeared normal. He was said to have sat up at 5 months.

X-ray showed the sagittal suture to be closed and the coronal sutures almost closed. Bone age was normal.

Operation was performed by Dr. Frederick Fender on Oct. 9, 1939, when the patient was 8½ months old. The anterior fontanel was found to be obliterated. A strip of bone 1 cm. wide was excised along the line of the two coronal sutures from one sphenoid to the other and another strip of bone 1.5 cm. wide was excised, connecting the first with the lambdoid to the right of the midline parallel with the fused sagittal suture. Transfusion of 150 c.c. of blood was given at the end of the operation. The postoperative course was uneventful. X-ray on Oct. 16, seven days after operation, showed the coronal channels to be 1.3 cm., and the sagittal channel to be 2.6 cm. in width; the former were slightly and the latter much wider than at the time of operation. He was dismissed October 20. At this time the circumference of the head was 49.25 cm., an increase of 0.75 cm. since operation. The cephalic index was 0.74.

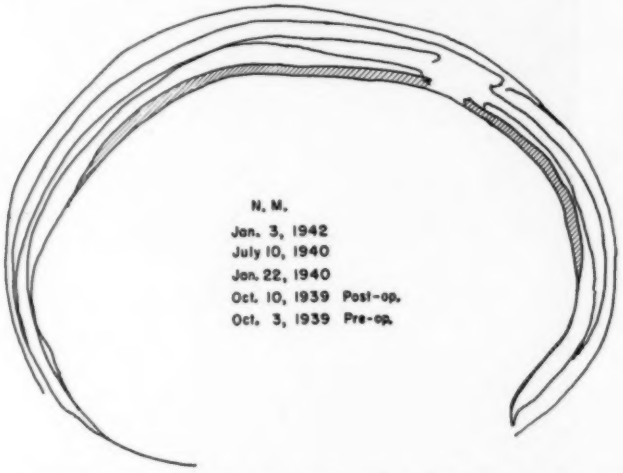

Fig. 14.—Case 4 (N. L. M.). Superimposed tracings from x-rays. The shaded area shows the expansion that occurred within twenty-four hours after operation. Growth of the skull appears to have been uniform and evenly distributed since operation.

On Jan. 22, 1940, the head circumference had increased by 0.75 cm. to 50 cm. X-ray showed a symmetrical enlargement of 1 cm. in length and 0.5 cm. in breadth. The operative channels were of about the same width as on October 16, but the edges were fuzzy, and remineralization was beginning to appear. There were no complaints.

On June 10, 1940, x-ray showed another increase of 1 cm. in length and 0.5 cm. in breadth. The sagittal channel was now about 2 cm. in width, but the coronal gaps were about the same width as before. New bone had been laid down in increasing amounts, less in the coronals; however, near the posterior end of the sagittal excision, just above the lambdoid suture, three small lacunae were visible. There were no complaints and development appeared normal.

On Jan. 22, 1941, at the age of 2 years, x-ray showed further increases in the skull outlines of 4 mm. in width and 8 mm. in length. The sagittal channel was nearly filled with new bone, except in the lacunae, which were still visible, and the inner table was still interrupted. The coronals, however, were still as wide as on Oct. 16, 1939, distinct throughout, with only slight remineralization near the vertex.

On March 6, 1941, he was admitted for cervical abscess. No complaints referable to the cranial synostosis were elicited. The neurologic examination was negative, and the fundi were normal.

On July 29, 1941, the head circumference was 52 cm.

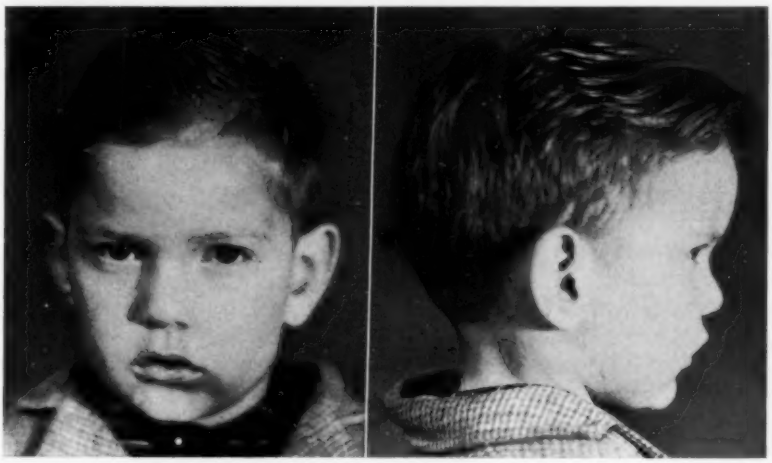

Fig. 15.—Case 4 (N. L. M.). Feb. 5, 1942, at age of 3 years, two years, four months after operation. The child's appearance is not notably abnormal. There is no proptosis.

On Jan. 3, 1942, x-ray showed the skull dimensions to be about the same as the previous year except that the vertical height was about 2 mm. greater. The sagittal gap was still visible, though nearly filled in, and the inner table appeared thin; the lacunae at its posterior end were still present. The coronal channels showed considerable new bone except at the vertex, where they were quite thin, but could be plainly seen throughout and were of the same width as since operation. The appearance of the skull was still definitely abnormal, though not remarkably so, with characteristics of tower skull. The cephalic index was 0.73.

On Feb. 4, 1942 (at age of 3 years), photographs were taken. His appearance was not grossly abnormal. Careful examination of the fundi showed no fullness of the retinal veins, good cupping, and sharp outlines of the discs. The child was too young for accurate visual tests. No complaints were elicited.

Case 5.—J. F., a male patient of Dr. Roland P. Seitz of San Francisco, was born Sept. 28, 1941. Malformation of the head was noted at the time of birth. The forehead was high and rounded and the occipital region was long and narrow, resembling the bow of a boat. A ridge was felt over the position of the sagittal suture, extending from the anterior to the posterior fontanel. X-rays taken on Nov. 19, 1941, showed the posterior 10 cm. of the sagittal suture to be completely closed; the coronal and lambdoid sutures were open. On December 2, the forehead

was found to be bulging, and the protrusion of the occipital region had increased. Viewing the head from above, the width was about normal back to the coronal suture, and from there it progressively narrowed back to the lambdoid suture.

Operation by one of us (E. B. T.) was performed on Dec. 10, 1941. A strip of bone about 15 mm. wide was removed from the left parietal bone, beginning at the

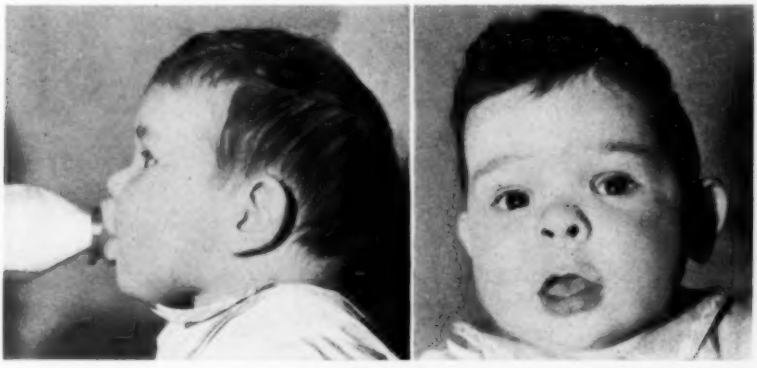

Fig. 16.—Case 5 (J. F.). March 23, 1942, fourteen weeks after operation. The appearance is essentially normal.

Fig. 17.—Case 5 (J. F.). Superimposed profile tracings from x-rays. The immediate postoperative expansion of the parietal region is striking. Note further growth of the skull and rounding of the parietal region in the last tracing.

anterior fontanel and going back to the lambdoidal suture; thence across the sinus into the right parietal bone, and a similar strip, 10 to 12 mm. wide, was removed from the right parietal bone from the lambdoid suture to the anterior fontanel. The result was to isolate the sagittal suture. Both parietal bones could be sprung. This was the first of our operations in which a double excision was done. Postoperative recovery was uneventful.

While too little time has elapsed since operation to permit final judgment, a remarkable expansion of the skull has already occurred in the parietal region which

is well seen in the tracings from successive x-ray pictures and also in the photographs. The difference in profile that occurred within six days after operation is particularly striking. Growth of the skull as a whole appears to be normal. The cosmetic improvement is shown in the photographs. When last examined on March 23, the bony defects were closing, as determined by palpation.

DISCUSSION

The number of cases in this series is too small to permit us to assess fully the general value of the operation and its limitations. While, therefore, our conclusions must be regarded as tentative, we believe the results to be at least encouraging and the observations to be of some interest.

An almost immediate expansion of the skull along the lines of excision, as shown by measurements and profile tracings, was observed in four of the five patients and probably occurred also in the fifth, suggesting that abnormal stresses had already been set up. In four patients the operative gap continued to widen considerably for a period of months, and in two patients it remained open in part for still longer periods, up to eleven years in one patient (V. G.). New bone formation became visible in four patients in about four months, but the area of excision remained visible either as a thin area in both tables of the skull or as an actual interruption in continuity of the inner table throughout the entire period of observation. That the persistent thinness of the cranium (lasting sixteen and one-half years in one case) may have acted as a safety valve is suggested by the occurrence of some elevation of the skull at that location in one patient and by the appearance in two patients of increased convolutional markings some years later without clinical evidences of increased intracranial pressure such as headaches, papilledema, reduced vision, mental deterioration, or convulsions. It is notable that in three of our patients, intelligence has been of superior grade. The cosmetic results are also encouraging. The appearance has improved in all cases, and while some deformity is still visible, it is not conspicuous in either and does not constitute any notable handicap to the children. Without operation we believe that deformity would have been severe in all of them and that serious pressure sequelae would probably have occurred in at least three. In two of the patients closure of both coronal and sagittal sutures was present, a combination in which loss of vision and mental deterioration are very common, and convulsions sometimes occur. In one patient closure of the coronals was present with great deformity, and pressure sequelae would not have been unlikely. In the two patients with sagittal closure only, pressure sequelae were probably less likely but not impossible. We are inclined to believe that somewhat better cosmetic results might have been obtained by earlier operation in the two cases (N. L. M. and V. G.) in which surgical interference occurred at an age of a little over 8 months.

It will be noted that the operation was not repeated in any of our cases. This might conceivably be necessary or desirable if the first

operation failed to prevent pressure effects of serious degree at some later date, and we see no good reason why, in such cases, it should not be done. None of our patients has had indications for a repetition.

Although we published our first paper fifteen years ago, the preventive, early operation has attracted little attention, and we know of no other publications in which it has been reported in infancy. On the other hand, there are several papers in which late, palliative operations have been reported in cases of long-standing in which increased intracranial pressure had already produced largely irreparable damage to vision or intelligence or both, and in which exophthalmos and cranial deformity had become extreme. It can hardly be expected that such operations as subtemporal decompression,[2b] Bauer's[2c] uncapping procedure, or King's[2e] "morcellation" could accomplish more than the relief of intracranial hypertension, the reduction of deformity, and sometimes the cessation of convulsive seizures; marked improvement of vision and mental deficiency can hardly be expected, a view which is borne out by Woodhall's[10] recent report of five cases treated by King's operation. Naturally, if cases are advanced to this late stage, palliative operation is indicated and should be done, but, in our opinion, early recognition in infancy and early operation are far preferable.

It seems likely that the medical profession has hesitated to accept the operation partly because of old prejudices based on the fact that it was done some five decades ago[11, 12] for incorrect indications (mental deficiency) for which it failed, and partly because of certain theoretical objections to the supposed possibility of restoring or creating physiologically functioning sutures by linear craniectomy. Rubin[13] expresses the objection as follows: "The operation for the production of artificial sutures seems unsound. It is based on the belief that if the synostosed area were removed, bone growth would then proceed at a normal rate. Since lateral bone growth is a function not of the bone itself but of the interstitial suture substance, it can be understood why this operation would be fruitless." We quite agree that the artificial production of true sutures is an impossibility, and we have not expected that the areas of bone excision would function as sutures. What we believe can be accomplished is substitution for the closed sutures of temporary (though fairly long persistent) zones of free expansion paralleling normal suture lines and the creation in the same places, after recalcification, of more permanent areas of thin cranial bone which can continue to serve a decompressive function for many years. Done as early as we have advised, the results aimed at are a lessening of deformity and particularly the avoidance of the more serious effects of chronic intracranial hypertension. The results actually noted in our patients, such as the immediate postoperative and later continuing expansion of the skull, its reasonably normal growth, the absence of proptosis, papilledema, optic atrophy and visual defects, and mental deterioration, suggest that the purposes of the operation can actually be attained.

We feel justified in believing that the method is sound enough in principle and that the potential dangers of premature synostosis are serious enough to outweigh heavily the risks of the operation, which are not great. The only alternative choice is to do nothing in the hope that the patient may escape blindness, lagophthalmos, mental deficiency, convulsive seizures, and a severe cosmetic handicap. The chances that he will escape part or all of these appears from a survey of the literature to be poor.

Early recognition of the cases, at a period of life when preventive operation is feasible, is largely in the hands of the pediatrician and, as a rule, is easy even in the first days or weeks of life. Not uncommonly, mothers call the doctor's attention to the deformity of the head as a whole or to the sagittal ridge. Since, in early infancy, the disorder is asymptomatic, the temptation is to do nothing and await developments. In our opinion, it is the pediatrician's responsibility to consider surgical intervention and the surgeon's responsibility to be aware of its feasibility.

SUMMARY

Five cases are reported in which linear craniectomy was performed during infancy on patients with premature synostosis of the cranial sutures for the purpose of preventing the common late sequelae of increased intracranial pressure and severe deformity. The results obtained would appear to be encouraging.

CONCLUSIONS

1. For premature synostosis of the cranial sutures, excision of strips of bone parallel to the closed suture or sutures is desirable.

2. The operation should be performed in infancy, preferably at or before the age of 6 months. The age of about 10 weeks is optimal.

3. By early operation, loss of vision and other serious sequelae may be prevented.

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WESTERN EQUINE ENCEPHALOMYELITIS IN INFANTS

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DURING August, 1941, in a period of a little more than two weeks, several cases of apparently proved Western equine encephalomyelitis were seen in infants under 1 year of age. These cases occurred during the course of an outbreak of human equine encephalitis in Manitoba which comprised a total of 509 cases. Twenty-seven of these were in infants under 1 year of age. Seventeen of these infants have been studied at the Children's Hospital of Winnipeg and are the subject of this report. It is noteworthy that encephalitis attacked particularly the very young and the very old. Forty cases were reported in children under 4 years of age. Twenty-seven of these were in infants under 1 year of age, nearly all of them less than 6 months old.

The epidemiologic observations made during this outbreak and also during an outbreak of acute anterior poliomyelitis which occurred at the same time and which totalled over 900 cases are reported by Donovan and Bowman.[1]

References to equine encephalitis in infants are few in number. In 1938 an outbreak of Eastern equine encephalitis occurred in the Eastern states among horses. Shortly afterwards cases appeared among human beings. Eight cases occurred in children, seven of them in infants under 19 months of age. Five died and the three survivors were left with serious neurologic sequelae. All these cases were proved by neutralization tests to be cases of Eastern equine encephalitis. The Eastern virus was isolated from the five infants who died and from the brains of six horses dead of the disease. In the same year there was an outbreak of Western equine encephalitis in Saskatchewan reported by Gareau[2] and Fulton.[3] There were twenty-nine cases, seven of them in children under 12 years of age. There were four deaths of which one occurred in an infant. There were eighteen complete and seven incomplete recoveries. Fulton isolated the Western virus from the brain of an infant dead of the disease.

On the basis of the few cases reported from Massachusetts, California, and Saskatchewan, the Eastern disease seems to run a more acute course and is more often fatal than the Western.

In 1940 Davis[4] reported two cases of Western equine encephalomyelitis occurring in infants in California. In both cases permanent nervous sequelae, consisting of cerebral atrophy and mental deterioration, occurred.

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The cases of the infants which are the subject of this report are summarized in Table I. The infants in Cases 1 to 12 presented an almost identical clinical picture of fever, convulsions, bulging fontanel, generalized rigidity, increased globulin, and pleocytosis in the spinal fluid. All but two were proved to be cases of Western equine encephalitis by complement fixation test done at the Rockefeller Institute. All but the infant in Case 10 are known to have made a complete recovery and to have shown no sequelae after eight months as determined by my examination or by correspondence with the family physician. These cases are therefore presented as a single group and only one clinical history is given in detail.

The infants in Cases 13 to 17 comprise a group of cases showing sequelae after their acute infection, and these are reported individually. Two of these cases occurred in the newborn period. Two others have died eight months after their original infection.

GROUP I (CASES WITH NO SEQUELAE)

L. R. was a breast-fed baby aged 10 weeks. The only other child in the family was a boy of 8 years who has a congenital heart disease. The family history was otherwise negative. The baby was doing very well, weighed 12 pounds and had presented no difficulty whatever until the onset of the present illness. There was no history of acute illness in anyone living in or visiting the home. The baby had never been away from his home. His drinking water was always boiled, and the only other item in his diet was orange juice. The only other factors of epidemiologic interest are that he was badly bitten by mosquitoes which were very prevalent and aggressive about ten days before the onset of his illness. His hands were often covered with flies when he was out of doors, and it was not unusual for the baby to put his fists into his mouth.

On Aug. 11 the baby was restless and irritable. He had a mild diarrhea but no vomiting. He did not seem particularly ill. His temperature was 101° F., and there were no other noteworthy findings. It was particularly noted because of the mother's great anxiety about "paralysis" that Kernig's sign was negative and no rigidity of the neck was apparent.

Under moderate diet restriction the baby was reported to be much better on Aug. 13, although he still had a slight fever. On Aug. 14 the baby was very irritable but became very drowsy during the day and could not be awakened for feedings all afternoon. At 7 P.M. he was comatose, his temperature was 103° F. rectally, the anterior fontanel was obviously full and bulging, and there was generalized stiffness of a lead pipe variety in that the muscular stiffness yielded slowly to moderate sustained pressure. There were no convulsions.

The baby was taken to the Children's Hospital. Spinal puncture revealed a clear fluid under greatly increased pressure. There were 445 cells of which 75 per cent were polymorphonuclears. Sugar and chloride estimations were not done.

During the succeeding forty-eight hours the baby's condition was critical. He had repeated severe generalized convulsions which could not be controlled satisfactorily by any type of sedation. Generalized stiffness was marked. Feedings had to be administered by nasal tube, since sucking and swallowing were both impossible. Maternal blood serum was given intramuscularly on the day of admission, and sulfathiazole was given in small doses for three days.

On the third hospital day the temperature began to drop, the convulsions ceased, and the baby began to take the breast again. By the fifth hospital day he seemed considerably better except for some residual stiffness. Recovery was very rapid,

TABLE I

CLINICAL SUMMARY OF CASES OF WESTERN EQUINE ENCEPHALOMYELITIS IN INFANTS

CASE	NAME	AGE (WK.)	SEX	FEEDING	ONSET	FEVER	CONV.	RIGIDITY	C. S. FLUID GLOB.	C. S. FLUID CELLS	LAB. TEST FOR W.E.E.	DATE OF TEST	PRESENT STATUS
1	L. R.	11	M	BR	8/11/41	x x	xxx	xxx	xx	445	x 1.16 CF	10/29/41	Recovered
2	A. Mck.	14	M	BR	8/14/41	x x	xxx	xxx	xx	118	Not taken		Recovered
3	H. K.	20	M	BO	8/16/41	xx	xx	xx		343	x 1. 8 CF x 1.16 CF x CF	8/22/41 9/ 6/41 10/14/41	Recovered
4	J. C.	5	M	BR	8/14/41	xx	xxx	xxx	xx	1400 15	x CF	8/16/41	Recovered
5	C. S.	8	F	BR	8/17/41	xx	xxx	xx	x	Bloody tap	–	8/22/41	Recovered
6	K. K.	8	M	BR	8/12/41	xx	xxx	xx	x	Bloody tap	x CF	10/30/41	Recovered
7	J. B.	6	M	BR	8/18/41	x	xxx	xx	x	998	– CF x CF x N	8/22/41 9/ 6/41 10/ 7/41	Recovered
8	R. S.	5	M	BR	8/12/41	x	xx	xx	x	Bloody tap	x CF	8/25/41	Recovered
9	D. M.	40	F	BR	8/11/41	x	xx	xx	–	145	x CF	8/25/41	Recovered
10	J. B.	6	F	BR	8/ 4/41	x	xx	xxx			x CF	8/17/41	Not known
11	J. S.	76	F	BO	8/?15/41						x CF		Recovered
12	L. C.	12	M	?	8/23/41	x	xx	xxx	x	393	x CF		Recovered
13	H. D.	52	F	BO	8/ 6/41	xx	xxx	xxx	?	150	x CF	10/ 9/41	Spasticity left arm and leg
14	G. S.	1	M	BR	8/18/41	xx	xxx	xxx	?		x N	3/ /42	Spastic diplegia; cortical atrophy
15	J. S.	1	M	BR	8/ 7/41	xx	xxx	xx	?	?	x CF x CF	3/ /42 7/16/42	Spastic diplegia; microcephaly
16	I. W.	6	F	BO	7/16/41	xx	xx	xx	x	106	Not done	Not done	Died 3/28/42; apparently well in interval
17	S. R.	4	M	?	7/ 2/41	xx	xxx	xxx	x	63	x CF	8/10/41	Spastic diplegia; died 4/42

W. E. E., Western equine encephalitis.
BR, Breast fed.
BO, Bottle fed.
CF, Complement fixation.
N, Neutralization test.
x Positive.

and he was discharged on the twelfth day. Blood was taken from the baby and mother for complement fixation. The baby's blood was reported positive for Western equine encephalomyelitis. The mother's blood was negative.

This baby is almost a year old now. He sits well, stands, and behaves normally in every way.

In Table I the main clinical features of the eleven infants who were seen in the acute stage of the disease are summarized. Several interesting facts are noteworthy. Almost all the babies were *breast fed.* This led to the speculation that perhaps the mother might be a factor in the epidemiology of this condition. Maternal serum was given to three babies in the hope that the mother's blood might possess sufficient antivirus to be of therapeutic value. However, in three cases where maternal blood was examined for neutralizing bodies, the report was negative in each instance.

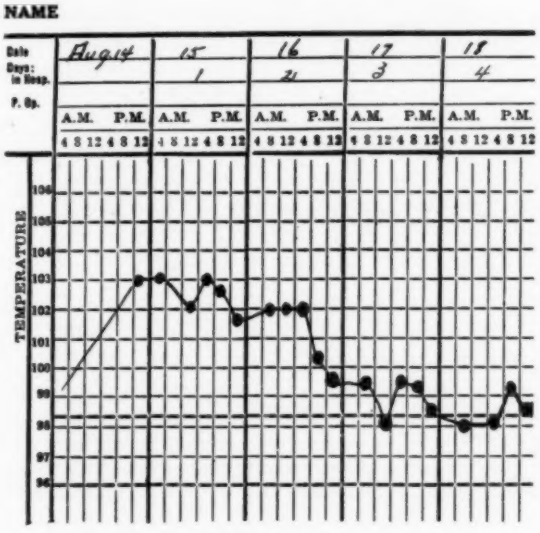

Fig. 1.—Temperature curve of L. R.

The *temperature curve* (Fig. 1) obtained in each infant showed a consistently high temperature on admission and this level was maintained for about forty-eight hours, when the temperature fell rapidly to normal and remained normal. The fall of temperature corresponded to the cessation of convulsions and a rapid improvement in the infant's condition so that a baby who was almost moribund in the evening seemed almost completely recovered by morning.

As noted before, a peculiar type of *rigidity* was present in all the babies. It was one of the first clinical signs to appear and the last to disappear. One baby had some residual stiffness several weeks after the acute illness had passed. The character of this rigidity is perhaps

best described as of the lead pipe variety in that there was no real spasticity but a gradual yielding of the stiffened limb to moderately firm continued pressure.

Convulsions were present in all the babies and were more severe and continued for a longer period than one could imagine possible without a fatal outcome. Various methods of controlling these convulsions were tried but all with very little success.

Feeding in nearly every case was by gavage, since swallowing and sucking seemed impossible.

The spinal fluid whenever it was satisfactorily obtained showed a cell count usually over 100 cells and in one case up to 1,400 cells. In this last infant the count was repeated on the third day, just as improvement was becoming evident, and the count had dropped to 15 cells.

Treatment in every infant consisted of gavage feeding and general nursing care. Maternal serum was administered to three infants, but no difference was noted between their clinical course and that of the infants who did not receive the serum. Sulfathiazole was given to some of the infants mainly because of the fear of pneumonia developing as a complication, as it had in reported cases of St. Louis encephalitis. It did not seem to influence the course of the disease. None of the infants developed clinical evidence of pneumonia, and those who did not receive sulfathiazole progressed as favorably as those who did.

GROUP II (CASES WITH SEQUELAE)

This group consists of infants who have developed sequelae in the form of mental retardation and spasticity (see Table I, Cases 13 to 17). The case histories of these infants are presented below:

CASE 13.—H. D., female, aged 1 year, was taken ill on Aug. 6, 1941, with fever and drowsiness. The next day she had a convulsion and a temperature of 105° F. On Aug. 8 her spinal fluid was examined and said to be "positive for infantile paralysis." The cell count was reported to be 150 cells. She was in continuous convulsions when she was brought into the city. She improved after a few days and was transferred to the Children's Hospital. It was noted on her discharge from the Infectious Hospital that she could not use her left leg and arm, and these were put up in splints.

On admission to the Children's Hospital sixteen days after the onset of her illness, her left leg and arm were markedly spastic. Her blood was reported positive for Western equine encephalitis on Oct. 9, 1941. When last seen in March, 1942, there was still some spasticity, although definite improvement had occurred and her mental status appeared to be normal.

The error in the original diagnosis is understandable when one realizes that two epidemics were at their peaks at the same time, and the nature of the acute cerebral infection occurring in the infants was not fully appreciated until complement fixation and neutralization test reports on the infant's blood demonstrated the presence of encephalitis in the community.

CASE 14.—G. S., aged 7 months, was brought in for examination by me because of generalized spasticity and mental retardation. He was born during the second week of August. Delivery was normal, although the mother had headache and

fever a few days post partum. On the third day of life the baby developed a temperature of 104° F. and generalized convulsions. This continued for forty-eight hours and was followed by several days during which the baby was listless and took little food. Apparent recovery then took place for a while, but it soon became evident that the baby was holding itself stiffly and the head was retracted. There was difficulty in swallowing food. On examination at 7 months of age the baby was in marked opisthotonus (Fig. 2). Rigidity was generalized. Weight

A.

B.

Fig. 2.—Case 14 (G. S.). *A*, Shows marked spasticity and opisthotonus at 7 months of age. *B*, Fever and convulsions at four days of age. Positive complement fixation for Western equine encephalitis.

was 15 pounds. Circumference of head was sixteen inches, and the anterior fontanel admitted two fingers. Vision was poor. Spinal puncture was negative. Mantoux was negative. Encephalography was done and revealed (Fig. 3) cortical atrophy and dilatation of the ventricular system. Blood was taken from the baby and parents. This was reported positive for Western equine encephalitis on the baby's and mother's samples and negative on the father's blood by neutralization tests done by Dr. Cox at Hamilton, Montana.

It should be noted that the neutralization test was positive seven months after the acute illness. It is felt that any infant presenting the picture of mental retardation, spasticity, or seizures and especially with a history of an acute febrile episode in early infancy should have a neutralization test done for equine encephalitis.

CASE 15.—J. S., born in Regina, Saskatchewan, Aug. 7, 1941, premature two to three weeks, and weighing 6 pounds, 4 ounces. The labor was not unusual; the cord was around the neck, but there was no cyanosis after birth and his condition was regarded as satisfactory until his fourth day when he refused to nurse and had a temperature of 103.2° F. The next day he was listless and drowsy. A spinal puncture was done, and a bloody tap was obtained so that no cell count was possible. The next day the baby had convulsive seizures and was seen by Dr. Gareau who felt that convulsions were the result of an acute infection. The baby was given Kavitan intramuscularly and full doses of calcium gluconate. A leucocyte count done on Aug. 12 showed 23,500 cells. The high fever and convulsions continued for three days, following which there was rapid improvement, and the baby began to feed and cry normally. It is noteworthy that the mother also had an infection post partum which was regarded as respiratory in origin.

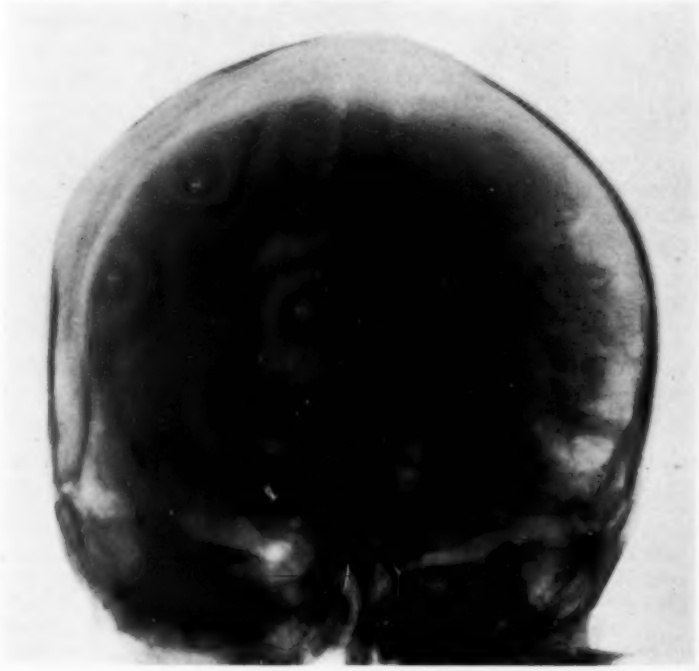

FIG. 3.—Encephalogram of G. S. (Case 14), showing left cortical atrophy and ventricular dilatation.

At the age of 6 months this baby was admitted to the Children's Hospital under the care of Dr. G. H. Shapera. There had been no further convulsive seizures, and the baby had been breast fed. A weakness of the left foot developed, and a cast was applied. On examination at 6 months of age the baby was obviously not developing normally. His head was retracted, and there was a spastic paralysis involving all his extremities. He had difficulty in swallowing, and there was a respiratory stridor. Spinal puncture, Wassermann reaction, and tuberculin test were all negative. Circumference of head was fifteen inches and the fontanel was closed. Blood was taken for complement fixation test from mother and baby. The

report received from Dr. Casals of the Rockefeller Institute showed the baby's blood to be positive for Western equine encephalitis in a 1:16 dilution and the mother's positive in a 1:4 dilution.

It will be noted that the history and findings in Cases 14 and 15 are identical. In both cases mother and baby both had a febrile illness, and both showed laboratory evidence of Western equine encephalitis.

The route of infection in both these cases would seem to be from mother to baby either through the placenta or by direct contact post partum. It is unlikely that infection by an insect vector could occur in the maternity ward of a hospital. These were the only cases encountered in the newborn infant, and these were the only mothers whose blood was positive. We have not been able to find similar reports in the literature.

CASE 16.—I. W. was admitted to the Children's Hospital on July 16, 1941, at the age of 6 weeks with a history of fever and convulsions. Spinal puncture was done, and the fluid was found to contain 106 cells. The convulsions lasted about forty-eight hours, following which the baby made a good recovery. Blood was not examined for neutralizing bodies as the true nature of the condition was not suspected. After being apparently well for eight months, the baby was readmitted to the Children's Hospital March 28, 1942, with a history of fever and cough for five days. Death occurred within a few minutes of admission and a post-mortem examination was done. A full report of this case with post-mortem findings will be published later.

CASE 17.—S. R. developed fever and convulsions at the age of 1 month (Aug. 2, 1941). Spinal fluid showed 63 cells. A few days later it was noted by his parents that his neck was stiff and retracted. On examination three months after the acute illness he had generalized spasticity and early optic atrophy. Blood examination was positive for Western equine encephalitis. The baby was reported to have died March, 1942, of an acute gastrointestinal infection. It was not possible to obtain permission for an autopsy.

DIFFERENTIAL DIAGNOSIS

It was immediately obvious that we were dealing with an acute infection of the central nervous system. It also became apparent within a few days, as these infants came in one after another with an identical clinical picture, that we were dealing with an outbreak of epidemic proportions. Because of the prevalence of poliomyelitis, a few of the conditions of these infants were diagnosed as such, and it was felt by some that we were dealing with a cerebral form of poliomyelitis. The possibility of equine encephalitis was considered, but it was not possible to establish this diagnosis on clinical grounds alone.

The correct diagnosis was made several days or weeks later when blood was examined from these infants by Dr. Casals of the Rockefeller Institute in New York, using the complement fixation method for Western equine encephalitis, Eastern equine encephalitis, St. Louis encephalitis, and lymphocytic choriomeningitis, and by Dr. Cox in the

Public Health Laboratory at Hamilton, Montana, by the neutralization method for Western equine encephalitis and Eastern equine encephalitis. Of ten infants seen in the acute stage, nine were positive by complement fixation. One of these was also positive by neutralization test. The lone negative was on a blood sample taken on the fifth day of illness. It has not been possible to repeat this examination to date. Thirty-five infants with proved poliomyelitis were used as controls. Thirty-four were reported negative. This is significant since the percentage of the population whose blood contains antibodies for Western equine encephalitis is unknown, and, in view of the outbreak in 1938, it was felt that there was a possibility of a considerable number of false positives. In addition, although the histories were carefully gone into, not a single case of possible exposure to horses was found, and the possibility of human carriers had to be considered. It was therefore interesting to find that examination of the blood of three of the nursing mothers concerned was negative.

One very interesting case from the point of view of the time of taking blood samples was J. B. This 6-week-old nursing baby took sick Aug. 18. He had high fever and convulsions on Aug. 20 and 21. There were 998 cells in the spinal fluid. He was critically ill, but as in the case of the others in this group, he made a rapid and apparently complete recovery.

Specimen 1 taken Aug. 22 was negative by complement fixation.
Specimen 2 taken Sept. 6 was positive to Western equine encephalitis.
Specimen 3 taken Oct. 2 was positive by neutralization test 1:1000 dilution.
Spinal fluid drawn on Aug. 19: virus recovered on intracerebral injection into guinea pig; identified as virus of Western equine encephalitis by Dr. Cox.

In some of the cases reported the correct diagnosis was made several months after the acute illness by means of the laboratory methods mentioned above. The original diagnosis was usually poliomyelitis or influenza, or else the illness was not considered severe enough to justify seeing a doctor. It is likely that this group will be greatly augmented in the future.

It would appear from our experience that in any infant showing mental retardation, convulsions of unknown origin, or spasticity and giving a history of an acute febrile illness in August or September, 1941, the possibility of Western equine encephalitis should be considered seriously and blood samples taken for examination, using one of the methods referred to above.

Much of the interest in any study of encephalitis in infants lies in the end results observed. From this angle this report can only be of an interim nature, since barely eight months have elapsed since the outbreak. Reports of follow-up studies on equine encephalitis in infants

are almost nonexistent. The Boston report on the 1938 outbreak of Eastern equine encephalitis has been referred to. All the survivors showed sequelae in the nature of mental retardation and spasticity. The brain apparently showed a great increase in the size of the ventricles as proved by encephalography and a decrease of total size as shown by overriding of sutures and actual measurement. The reports of Davis have been referred to.

Eleven and probably twelve of our infants have so far made a complete recovery. Further observations will be carried out. In appraising the mental status of these infants, we are planning to use a standard method, and the form outlined by Gessell has been adopted. It is our intention to have these infants checked over from time to time by a competent psychiatrist as well as a pediatrician. In this way it should be possible to have a report of scientific value in the course of the next few years.

Two deaths are reported, and both of these occurred eight months after the acute infection. Only one of these can so far be regarded as a proved case. This infant did not die of his disease, but he did have spasticity and mental retardation as a result of his encephalitis. The other infant cannot be regarded as a definite case until a full autopsy report and result of examination for virus are available.

The two cases occurring in newborn infants are regarded as being of unusual interest. The correct diagnosis would probably never have been made but for the fact that we now routinely consider the diagnosis of equine encephalitis in an infant showing mental retardation and spasticity. In both of these cases there was also the history of an acute cerebral episode occurring during the middle of August, 1941, when practically all our cases were seen. These two cases also raise some interesting epidemiologic problems. The fact that the blood of both mother and baby was positive for Western equine encephalitis and that both had their acute illness on the fourth or fifth post-partum day suggests the possibility of prenatal transfer of the virus to the infant. Contact infection post partum is considered unlikely in view of our experience with other nursing babies who developed their infection later in life and who showed positive complement fixation tests whereas the blood of their mothers was negative by the same technique. The opportunities for contact infection are surely as great in a nursing baby at home as in the hospital.

SUMMARY

1. A clinical report based on a study of seventeen cases of Western equine encephalomyelitis in infants is presented.

2. Twelve have made a complete recovery; five have developed sequelae.

3. Two cases of Western equine encephalomyelitis of the newborn infant are included in this series.

4. The necessity for considering the diagnosis of equine encephalomyelitis in infants showing spasticity and mental retardation is noted.

5. A further study of the late effects of this disease is under way and will be the subject of a later report.

The assistance of Dr. Doris Menzer in tracing possible sources of infection is gratefully acknowledged.

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PROPHYLACTIC USE OF SULFANYLGUANIDINE IN A DYSENTERY OUTBREAK

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IN VIEW of the recent addition of sulfanylguanidine to the list of effective chemotherapeutic agents, it is considered advisable to report the clinical results of its therapeutic and prophylactic use in an outbreak of bacillary dysentery.

Since the introduction of sulfanylguanidine by Marshall and coworkers,[1] encouraging results obtained in the treatment of dysentery lead to extensive study of its nature and clinical use.

The outstanding features of sulfanylguanidine as pointed out by Marshall and associates are as follows: (1) It is a sulfanilamide derivative which possesses a high degree of activity against various bacteria. (2) Absorption from the gastrointestinal tract is slight. (3) Water solubility distinguishes this drug from previously used intestinal antiseptics which depended on water insolubility for their action. (4) Toxicity is probably less, and certainly not greater than sulfapyridine and sulfathiazole. On the basis of these characteristics, the use of sulfanylguanidine in certain bacterial infections of the intestinal tract was given clinical trial by these investigators. They obtained very encouraging results in a group of patients with bacillary dysentery.[2]

Since this introduciton, the use of the drug in several series of patients with dysentery has been reported. Lyon[3, 4] treated a group of twenty-three infants and children suffering from an acute form of dysentery caused chiefly by the Flexner type of organism. Striking benefit was observed in this group when comparison was made with a control group of untreated children. Anderson and Cruickshank,[5] in Great Britain, achieved rapid and dramatic results in patients with severe cases treated early in the course of the disease. Their group comprised ninety-six adults with the Flexner type of bacillary dysentery, fifty-five of these serving as controls.

Although the drug has been used preoperatively as an intestinal antiseptic[6, 7] and in typhoid and dysentery carriers,[8, 9, 10] we have been unable to find reference to its prophylactic use in noninfected individuals during outbreaks of dysentery.

Its use in these individuals who have not been actually infected seemed at first glance not to be justified. From a practical standpoint, two facts modified this viewpoint. The first was that rapidly spreading outbreaks of dysentery, particularly those in institutions, frequently showed a high mortality. The second fact considered was that, while ideally therapy should be confined to sources of infection such as the dysentery

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patient or carrier, it has frequently been impossible to determine rapidly or accurately these sources. Stool cultures required time for identification and not infrequently failed to reveal the presence of the organism at all.

These difficulties appeared to outweigh the possible dangers from drug toxicity with the reservation that prolonged administration of sulfanylguanidine should be avoided until the subject of late toxic effects has been more completely investigated. For example, Daft and associates[11] have noted hyaline sclerosis of the blood vessels of rats receiving the drug. Other factors, such as abnormal dietary used in the experiments cited, might, however, have played an etiologic role. Corwin[12] has found sulfanylguanidine to be rapidly fatal in rabbits which die with renal, splenic, and hepatic lesions. Such lesions have not been observed in human beings, where the drug is neither well absorbed nor highly acetylated as it is in rabbits.

CLINICAL RESULTS

Prophylactic Use.—On Nov. 9, 1941, a 5-year-old girl in one of the scarlet fever buildings of the hospital developed fever, cramplike abdominal pain, and diarrhea with mucus and blood in the stools. The bed was immediately screened, stools and bedding disinfected, and the child established on a strict isolation technique, although stool cultures were negative for typhoid and dysentery organisms. Despite these precautions, a second case developed three days later. This was followed by an outbreak in three children, occurring on successive days in an adjoining cubicle. From the stools of two of these patients a dysentery organism was isolated by the City Laboratory. The organism proved to be a gram-negative nonmotile bacillus with the fermentative reactions of *Shigella dysenteriae* (Flexner) but failed to show consistent agglutination with any of the usual types of dysentery serum.

Three days later two more children developed fever, abdominal cramps, and diarrhea. These children were located in cubicles adjoining those in which the previous cases had developed. On Nov. 19, ten days after the first case had developed, eighteen new cases appeared in seven of the twelve cubicles in this immediate vicinity.

The problem which then confronted us was a serious one. The building at this time contained 118 children, all confined to bed with scarlet fever. These children were grouped in separate cubicles, each one accommodating from six to nine patients. The cubicles opened onto a hallway which ran the length of the building. Fortunately, all of the cases of dysentery had developed in cubicles in the north half of this building. This made it possible to staff this portion separately with its own nurses, attendants, and maids. By this complete isolation it was hoped to prevent the spread of the infection to the south half of the building which housed forty-eight patients.

The limitation of the spread to adjoining cubicles also gave an indication of the route of infection by narrowing the search for the source. It seemed unlikely that central kitchen, milk, or water supply contamination would involve only the patients in the north half of a single building, and this was borne out by the failure to culture organisms from water, ice, and food. Further investigation failed to reveal any of the ward personnel with gastrointestinal symptoms except one person who had a mild transient diarrhea. Examination of the stool in this case proved negative for dysentery organisms, and the loose stools subsided in less than twenty-four hours.

Flies present in the building were trapped and cultured for dysentery organisms with negative results.

It thus appeared that infection was spreading from patient to patient, this supposition being more definitely demonstrated by the future course of the outbreak. We felt that the patients in this area where the spread was occurring were in great danger of developing dysentery superimposed on scarlet fever, and serious results with possible fatalities were anticipated. For this reason the forty-five children exposed in the north half of the building, thirty of them being from cubicles in which a case of dysentery had developed, were given a prophylactic course of sulfanylguanidine. This course consisted of the administration of 0.05 Gm. per kilogram of body weight every four hours for one day, then every eight hours for two days.

The results were most gratifying. No cases of dysentery developed in this group of forty-five patients. One patient developed slight fever with four stools two days after the institution of sulfanylguanidine but failed to show mucus, blood, or dysentery organisms.

As previously mentioned, the south wing of the ward had been considered protected by its segregation from the north wing (infected wing) of the ward. In this group of patients who were not given a prophylactic course of the drug, four cases of dysentery did develop during the succeeding five days. These patients who developed the disease were immediately treated with sulfanylguanidine, and no further spread occurred.

Therapeutic Use.—A total of twenty-nine children between 2 and 12 years of age were treated. All showed fever, diarrhea, and mucus in the stools. Most showed blood and pus as well, but the dysentery organism was isolated in only four patients. The clinical diagnosis was confirmed in most of the remaining twenty-five patients by the demonstration of antibodies during the convalescent period. Eleven of the twenty of these patients whose serum was examined showed agglutination of the originally isolated bacilli at the end of ten days. Normal human serum failed to agglutinate these organisms. In other words, we were able to establish by the demonstration of subsequent antibody development that all children had been infected by the same organism, although it could usually not be found in the stools.

The first four cases of dysentery were characterized clinically by sudden onset with temperature ranging from 100 to 102° F., abdominal cramps, vomiting, and diarrhea with from five to ten stools daily. In these four patients, untreated, the diarrhea persisted unabated with mucus, blood, and pus for from five to six days.

In striking contrast, no patient receiving sulfanylguanidine from the onset had more than five stools daily for a longer period than two days! Indeed, in twenty-three of these twenty-five patients treated, the stools were reduced to less than five daily before twenty-four hours had elapsed. The average time for complete cure was three days in the treated group, while the four untreated patients had averaged eight days for cure. The benefit to the patients was so apparent that we did not feel justified in withholding the drug from more patients in order to give a larger control group. We also decided to give sulfanylguanidine to the original four patients after the disease had already progressed from five to seven days. These patients showed a prompt response, suggesting that sulfanylguanidine was effective therapeutically even when given comparatively late in the course of the disease.

The drug dosage employed followed the recommendations of Marshall and co-workers[2] and Lyon.[3] An initial dose of 0.1 Gm. per kilogram of body weight administered orally was followed at four-hour intervals by 0.05 Gm. per kilogram until the stools numbered less than five daily, then by the same dose of 0.05 Gm. per kilogram until formed stools had been present for from one to two days.

Two patients suffered a mild relapse after the drug had been discontinued, and its readministration was followed by prompt relief.

Dietary treatment of all cases consisted of weak tea, ripe banana, scraped apple, fruit juices, and, in a few cases, a kaolin-pectin mixture.

Absorption.—Blood sulfanylguanidine levels were determined in thirty patients within from twenty-four to forty-eight hours after the drug was started. These ranged from 1.2 to 9.5 mg. per 100 c.c. of blood, the level varying considerably despite uniform weight-dosage, as noted in Table I. An unusual feature was that blood levels of the same order were obtained regardless of whether an initial large dose was given or omitted. As would be expected, therapeutic results showed no direct correlation with the blood concentration of sulfanylguanidine, the action presumably taking place in the intestinal tract.

Toxicity.—Untoward results of therapy were negligible. Urinalyses and blood counts were performed in all cases. Of sixty patients, twenty-eight showed crystals in small amount in the urine, but no patient developed pain or gross or microscopic hematuria.

The blood erythrocytes and leucocytes did not become abnormal in number or morphology in any of these patients following the sulfanylguanidine administration.

One patient developed giant urticaria on the third day of drug administration. His blood sulfanylguanidine level at the time was 9.5 mg.

TABLE I

CHARACTERISTIC RESULTS OF SULFANYLGUANIDINE ADMINISTRATION IN A GROUP OF PATIENTS WITH DYSENTERY

PATIENT	AGE (YR.)	STOOLS LESS THAN FIVE (DAYS)	CURE (DAYS)	SULFANYL-GUANIDINE TOTAL DOSE (GM.)	SULFANYL-GUANIDINE LEVEL	TOXIC REACTION
M. McG.	6	1	3	20	2.6	None
K. A.	10	1	4	18.3	1.6	Crystalluria
S. L.	6	1	3	32	3.7	Crystalluria
B. B.	5	1	3	20	3.9	Crystalluria
J. C.	7	1	6	24.4	4.5	Crystalluria
B. G.	6	1	2	20	2.0	Crystalluria
J. McC.	9	1	2	31.3	6.2	Crystalluria
K. F.	7	2	4	27.7	6.0	Crystalluria
S. Z.	10	1	4	30	3.5	Crystalluria
M. M.	13	1	4	39	5.4	Crystalluria
E. D.	7	1	3	20	4.0	Vomiting
W. G.	2	1	2	13.8	2.5	None
J. G.	4	1	2	12	4.7	None
W. K.	13	1	4	44.3	1.2	None
J. M.	6	2	4	11	9.5	Urticaria
T. McC.	15	1	2	44.1	5.4	None
L. V.	5	1	2	20	5.5	None

per 100 c.c. (the highest level found in our patients). Another patient developed urticaria seven days after the cessation of therapy so that it was difficult to attribute this to the action of sulfanylguanidine.

All children tolerated the drug well except one who vomited once after being given 1.0 Gm.

These mild reactions were the only ones noted.

COMMENT

That sulfanylguanidine is a satisfactory therapeutic agent in certain forms of bacillary dysentery has been demonstrated by several workers. Our results appear to confirm their findings.

Recently Hardy and co-workers[9] have reported on the control of three epidemics of dysentery in a mental hospital, a military unit, and an institute for feeble-minded. They advocated the use of sulfanylguanidine in dysentery cases and in carriers discovered by the use of rectal swab technique and highly selective culture media.

It would seem from our results that it is sometimes necessary to go a step further to check immediately the spread of dysentery infection while the search for the source is being carried out. This prophylactic use of sulfanylguanidine would, of course, be a stopgap procedure to be discontinued as soon as the original source of infection, be it carrier, food, water, or insect, could be discovered and brought under control.

It should be stressed that we do not advocate the prophylactic use of sulfanylguanidine to replace general public health measures such as medical asepsis, the physical examination of employees, education of food handlers. In the case of the outbreak described, all of these measures had been instituted and in force at the time of the outbreak.

All employees are given a complete physical examination including Wassermann tests, stool cultures, and chest x-rays where indicated. All food handlers have been trained to report immediately minor illnesses or skin lesions and are constantly supervised in the performance of this duty. The rigid control of personnel has not been relaxed. It was still possible, however, for the outbreak to occur and develop alarmingly until the comparatively widespread use of the drug prophylaxis and therapy was adopted.

The therapeutic effectiveness of sulfanylguanidine was not questioned by members of our hospital staff, all of whom were enthusiastic about the results obtained. Whether the drug will prove equally effective in more severe forms of dysentery is not definitely answered, but indications from the workers cited before have been that it will be effective.

Its use suggests itself immediately in epidemic diarrhea of the new born infant, and undoubtedly reports of its use in this dreaded disease will be forthcoming.

CONCLUSIONS

1. An outbreak of bacillary dysentery occurred in a group of 118 hospital ward patients.

2. Forty-five patients intimately exposed to the disease were given a prophylactic course of sulfanylguanidine. None of these patients developed dysentery.

3. Forty-eight patients were less intimately exposed and not given a prophylactic course of sulfanylguanidine. Four of these patients developed dysentery.

4. Twenty-nine children who developed bacillary dysentery recovered promptly when treated with sulfanylguanidine.

5. Toxic reactions to the drug were negligible.

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SERUM PHOSPHATASE VALUES IN CHILDREN SHOWING RETARDATION IN OSSEOUS DEVELOPMENT AND LOW METABOLIC RATES

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AFTER searching for corroborating laboratory evidence to aid us in selecting patients who might be expected to improve under thyroid therapy, the reports of Talbot and associates[1, 2] were reviewed with considerable interest. That a laboratory test is needed which will give supporting information to the facts yielded by a study of the metabolic rate and osseous development of a hypothyroid child is understating the problem.

Creatine tolerance tests and serum cholesterol determinations have not helped us in our efforts to select patients who could be classified as hypothyroid individuals.

Talbot's recent work reveals the lack of uniformity of high cholesterol determinations in hypothyroidism. Seven of his patients were untreated cretins, yet the plasma cholesterol was reported under 185 mg. per cent. Five of this same group of cretins showed metabolism rates of minus 16 or lower, which demonstrates that patients with cretinism and low metabolism rates may fail to show high cholesterol values.

The report of Fan[3] indicated that the level of blood cholesterol and the degree of creatinuria did not parallel the basal metabolic rate before or after thyroid therapy.

Wilkins and Fleischmann[4] in a discussion of serum cholesterol values and creatine excretion in untreated hypothyroid children stated that the majority of children with hypothyroidism show serum cholesterol ranges from 250 to 600 mg. per cent compared with a range of 100 to 300 mg. per cent in normal children. Furthermore, the same authors state that in a hypothyroid child, cholesterol may fluctuate as much as 200 mg. per cent. It is obvious that reliance cannot be placed on a serum cholesterol determination unless it is very high. These authors also question the diagnostic value of creatine tolerance tests.

Poncher and associates[5] showed that the establishment of creatinuria, which is lacking in untreated cretinism, was continuous with maintenance of thyroid therapy. He concedes that it is not as convenient to carry out detailed creatine studies as it is to make certain other laboratory tests, i.e., serum cholesterol, but the latter did not prove to be satisfactory in his experience.

Most investigators agree that too much dependence should not be put upon the degree of osseous retardation alone. If rickets, syphilis, celiac disease, blood dyscrasias, and chronic infections or nutritional diseases

TABLE I

SHOWING CHRONOLOGIC AGE, SKELETAL AGE* BASAL METABOLIC RATE, AND SERUM PHOSPHATASE IN BODANSKY UNITS

NAME	CHRONOLOGIC AGE	SKELETAL AGE	B. M. R.	SERUM PHOS. (BODANSKY UNITS)
R. K.	6 yr., 6 mo.	6 yr., 6 mo.		2.6
M. B.	2 yr., 8 mo.	3 yr., 6 mo.		3.7
R. L.	9 mo.	Less than N.B.†		4.2
H. K.	5 yr., 9 mo.	4 yr., 9 mo.		4.8
L. D.	5 yr., 7 mo.	3 yr., 6 mo.		4.6
D. P.	6 yr., 5 mo.	4 yr., 9 mo.		4.4
C. H.	3 yr.	2 yr., 3 mo.		3.8
D. R.	10 days	Less than N.B.†		3.7
M. S.	5 yr., 10 mo.	5 yr.		4.6
G. B.	10 yr.	7 yr., 6 mo.		4.0
M. F.	4 yr., 3 mo.	2 yr., 3 mo.		3.5
J. D.	3 yr.	1 yr., 9 mo.		4.6
P. F.	6 yr., 11 mo.	4 yr., 3 mo.		3.8
T. B.	5 yr., 6 mo.	4 yr., 6 mo.		6.4
R. S.	4 yr.	1 yr., 3 mo.		6.8
R. B.	4 yr.	3 yr.		6.8
R. M.	7 yr., 6 mo.	7 yr., 3 mo.		6.0
R. M.	12 yr.	12 yr.		9.7
G. M.	4 yr., 6 mo.	4 yr., 5 mo.		5.3
T. H.	6 yr.	6 yr.		5.5
D. S.	1 yr., 9 mo.	1 yr., 9 mo.		5.8
M. C.	1 yr., 6 mo.	1 yr., 6 mo.		7.1
M. R.	11 yr., 6 mo.		-28	3.9
G. K.	11 yr., 10 mo.		-33	4.2
G. J.	7 yr.		-13	5.6
L. W.	12 yr.		-29	4.7
P. E.	6 yr.		-17	5.5
R. W.	6 yr., 6 mo.		-21	5.4
D. K.	5 yr., 3 mo.		-17	5.6
W. P.	8 yr.		-15	4.3
H. S.	13 yr.		-14	3.9

*Skeletal age was determined by comparing studies of carpal development with the standards found in the Todd's *Atlas of Skeletal Maturation*, 1937, The C. V. Mosby Co.

†N.B., Newborn.

can be ruled out, a delay of one year or more in bone development is significant, especially if accompanied by a low metabolic rate, high cholesterol, low creatine, or low serum phosphatase.

Table I shows that eleven out of fourteen children with definitely delayed osseous development had a serum phosphatase under five Bodansky units. Nine children with metabolic rates of minus 13 or below showed that the serum phosphatase ranged from 3.9 to 5.6 Bodansky units. Three children with delayed osseous development had serum phosphatase values ranging from 6.4 to 6.8 Bodansky units. Six children with normal osseous development showed ranges between 5.3 and 9.7 Bodansky units. Two children with normal osseous development had less than five Bodansky units. A group of ten control children (not shown in Table I) between 1 and 13 years of age with no apparent disease which might influence the serum phosphatase showed a range from 5 to 8.8 Bodansky units.

DISCUSSION

From the above data we find that twenty out of twenty-three children, who exhibited symptoms of mild hypometabolism clinically and who, in addition, showed either marked osseous retardation or low metabolic rates, also had serum phosphatase values of 5.6 Bodansky units or less, which is well under the average normal figure given by Bodansky as 7.5 units. Bodansky considered from 5 to 14 units as normal range in children. Talbot's normal range was from 4.5 to 12 units, with an average of 7.2 units.

Three children showing delayed bone development had values above 5.6 Bodansky units, but these (6.4, 6.8, 6.8) ranged somewhat less than the average normal values mentioned above.

The range found in fourteen out of sixteen (87.5 per cent) children used as controls was between 5 and 9.7 Bodansky units. The two children in this group with normal osseous development but low phosphatase values had symptoms which we believed to warrant a therapeutic test. After one month on thyroid therapy a recheck showed increased values of phosphatase approaching the normal range. Clinical improvement was likewise noted. These findings may be explained on the hypothesis that the hypometabolic process was of short duration and, therefore, not reflected by delay in carpal development.

We believe that the data presented reveals that serum phosphatase determinations give valuable supporting information, although not 100 per cent reliable, as frequently is the case with laboratory procedures when dealing with borderline problems.

While some overlapping does occur, the majority of our determinations fell low enough to be grouped in the abnormal range or high enough to place in the normal group.

Considered together with the clinical and other laboratory findings, corroborative evidence for or against a hypometabolic state was obtained in most cases.

This investigation bears out Poncher's assertion that no one laboratory test can be expected to make a diagnosis of hypothyroidism for us; we must evaluate all of the facts derived from clinical and laboratory examinations.

SUMMARY AND CONCLUSIONS

1. As a result of our observations, we believe that more value can be derived from the serum phosphatase determination than from serum or plasma cholesterol or the creatine tolerance tests in mild hypothyroidism. Undoubtedly a prolonged study of creatine excretion would be helpful, but we feel it is technically and economically impossible to carry out such studies in private pediatric practice. Therefore, a comparatively simple procedure such as the serum phosphatase determination should be given consideration as an aid in diagnosis when hypothyroidism is suspected.

2. We are encouraged to continue further observations on the serum phosphatase values, especially as it relates to mild hypometabolic problems.

3. Further data is being accumulated to show that the serum phosphatase values are a help in adjusting the optimum dosage of thyroid therapy. It was shown by Talbot that administration of thyroid therapy causes serum phosphatase to approach the normal range, and several of our cases (unpublished data) coincide with this observation.

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ASSESSING THE PHYSICAL CONDITION OF CHILDREN

III. The Components of Physical Status and Physical Progress and Their Evaluation

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ONE of the most interesting and, from the practical standpoint, one of the most advantageous properties of the Grid technique[1] of appraising the physical condition of children is that by which the several components of physical status and of physical progress may be individually measured and studied. The singular importance of being able to detect lagging development or a shift in nutritional grade before extensive changes in physique itself take place has been emphasized in previous papers[2, 3] dealing with the type of failure in growth and development which, if sufficiently continued, inevitably leads to ultimate malnutrition.

When the three components of physical status[1, 2] (physique, developmental level, and nutritional grade) are all under par, it is obvious that physical status itself will also be impaired. Generally speaking, a child so affected will be in a class whose physical condition is unsatisfactory according to almost any standard of comparison. Such a child (a B_3 or B_4) will clearly have passed the bounds of early recognition, with the consequences of delay still to be reckoned with. But even in these subjects, a clearer understanding of the mechanism of failing growth, as well as of what may reasonably be expected in recovery, can be obtained by analyzing the resultant physical breakdown into the constituent elements of physique, development, and nutritional grade at the moment of observation and at suitable intervals in follow-up.

While oncoming malnutrition affords a good working example of the importance that may be attached to the separate study and individual measurement of the three components of physical status, it is, quite definitely, a special case of those general phenomena in growth and development whose appraisal is also sought and required under other circumstances. Certainly one of the more puzzling questions that recurs at the bedside or, for that matter, at any physical examination is that which arises in the attempts to estimate, chiefly by inspection, how well nourished and how well developed a child is supposed to be and above all to distinguish clearly between what is assigned to or represented by the child's "nutrition" as compared or contrasted with what is represented by his "development." On the whole, clinical evidence of the state of nutrition as judged by the condition of the subcutaneous tissues, by the color and elasticity of the skin, and by other signs is much more definite

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than evidence on the state of physical development, in which, moreover matters of growth, body build, and even metabolism are blended, play their own part, and strike one observer in one way and another quite differently. These, to be sure, are vexing questions, but they enter into every assessment of physical condition, and the satisfactoriness of the result depends almost entirely on how clearly these contributing effects may be individually judged and agreed upon. So long, however, as matters of this kind must be handled chiefly on the basis of opinion and of experience, there is no likelihood of establishing a uniform scale of rating or of getting results that could be independently and uniformly repeated.

To every assessment of physical condition there are two parts: (1) measurement and (2) interpretation. A great deal of the difficulty that is encountered in the actual task of appraisal, as well as much of the dissatisfaction with the results that are ordinarily obtained, may be traced directly to the fact that clinicians have been obliged to apply to the problem of measurement a set of methods that are better suited to the problem of interpretation. To be sure, heights and weights have been measured, but they have been largely disregarded because there has heretofore been no method available for translating them into the attributes of physique, development, and nutritional grade that make up physical status and, in succession, physical progress; yet it is these attributes that enter into every appraisal.

The function and the properties of the Grid technique are thus concerned solely with the problem of measurement, and the results are thereby open to interpretation in accordance with the complementary findings of clinical examination, or again, with the judgment of clinical experience. But the basis of such judgment, where matters of growth and development are so directly concerned as they are in the problem of assessing the physical condition of children, must clearly be a systematic method of measuring the components both of physical status at any given observation and of physical progress for successive observations. In this way the chief burden that has heretofore been imposed on the clinician in attempting to judge what is called a child's nutrition is accepted instead by an objective method of measuring the relevant components of physical status, the results of which can then be put to interpretative review. In this way, also, the Grid technique seeks to accomplish the objectives which Clark, Sydenstricker, and Collins[4] expressed in the following paragraph:

> The increasing attention which is being given to child hygiene emphasizes more and more the need for some dependable index of physical fitness for practical use. It is unquestionably desirable that this index should (*a*) accurately indicate for the individual child his physical status, (*b*) be expressible in numerical terms, (*c*) be referable to a standard in order that significant deviations from health may be accurately measured, and (*d*) be simple and easily found for any child by persons without special training in health.

These are sound and desirable objectives, but it is not practicable to crowd all the required results into a single index of the ratio type, because the very nature of an index, in condensing the effect of several items into a single result, runs directly counter to the need for keeping separate and explicit track of relevant variables.

The main purpose of the present paper is, therefore, to give a more detailed account of the components that make up physical status on the one hand and of those of physical progress on the other. Wherever possible, photographic illustrations are employed to help convey the basic meanings that can be attached to physique, development, nutritional grade, and age, separately, and to show also how these may be reassembled for an assessment of the physical condition of children.

Fig. 1.—A group of children up for appraisal. Which of these can and which can not pass the test of growth and development by showing either satisfactory or unsatisfactory physical status and progress? What quantitative ratings can be given? Compare the heterogeneity of this arrangement with the regularity of that for the same subjects in Fig. 6, in which the two-dimensional array according to their Grid positions makes due allowance for the various combinations of physique and development they represent.

THE CLINICAL PROBLEM

To fix ideas, the nature of the problem which thus confronts the physician may be illustrated very concisely by the small group of children shown in Fig. 1. Such a school or clinic group will usually consist of children of various ages, sizes, and backgrounds. An almost infinite

variety of differences may be represented among them. But much that they possess in the way of physical attributes they will have in common, and some of their characteristics will be unique. In fact, a great and important part of the problem will consist specifically of the need for distinguishing between what is different and what is alike. What, for example, will it mean if two children turn out to have the same weight and age but different heights, or if they differ and agree in any other possible combination?

These questions, surely, belong to the problem, but they do not state the real and basic issues in it. To some, such a group of children would mean that the doctor is faced with the responsibility of deciding primarily whether each member conforms to acceptable standards of various physical traits. To others, the main objective would be to find, by one means or another, those of the group who are "below par"—who need attention, who should be helped by early recognition of physical faults and thus be referred for advice or even for special investigation or treatment.

A clearer understanding of what can and what cannot be accomplished in the matter of physical appraisals is contained in answers to a few specific questions: (1) How and to what extent does body build affect physical status in each child? (2) What does development contribute, and what is its relative share in the result? (3) Is nutritional grade optimal? (4) Is physique being lost or gained? (5) Is each child "on schedule" or, if not, which child shows lag, and which in that case can be confidently recognized as making up lag or which as failing to do so?

It is obvious that these questions cannot be satisfactorily answered simply by stating that one child is heavier or shorter than another or by listing individual heights and weights or, finally, by computing simply weight gains. They can, however, be answered on a uniform basis by obtaining the particular Grid ratings that apply to each question. In general, they are systematically dealt with in carrying out the two fundamental steps involved in appraisals by the Grid technique: (1) the evaluation of physical status and (2) the evaluation of physical progress.

I. THE EVALUATION OF PHYSICAL STATUS

Significance of Physique or Body Build

Owing to the fact, as already emphasized, that an individual child always represents some particular and simultaneous combination of physique, development, age, etc., within himself, it is impossible by subjective means to recognize the separate effects clearly. One can, however, distinguish the effect of a single variable, such as physique, by suitably arranging for comparisons among several children so that we control or, as statisticians say, hold the remaining attributes constant.

Fig. 2 illustrates this principle by portraying six children of different physique yet of approximately the *same* age and, from left to right, of almost exactly the *same* developmental level; namely, 78, 78, 79, 78, 78, and 76, respectively.

These children are grouped according to the positions of their height-weight points on the Grid. The boy is an A_2, the girls in the third channel removed from him are B_1's, and the remaining three are B_2, B_2-B_3, and B_3-B_4, respectively.

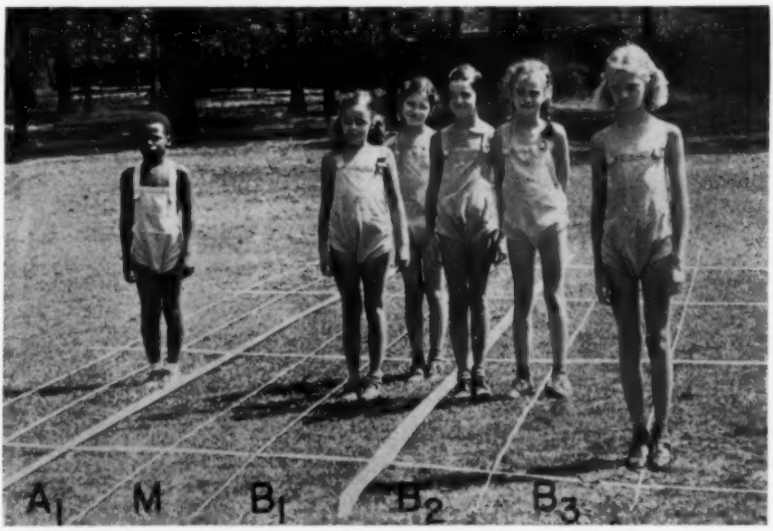

Fig. 2.—Showing characteristic differences in physique or body build for children at approximately the same developmental level in different channels. (From left to right A_2—78; B_1—78; B_1—79; B_2—78; B_2-B_3—78, and B_3-B_4—76.) Note the "husky" build of the boy in A with strong, well-rounded contours and how body lines gradually but nevertheless distinguishably pass over to the more slender and more angular types in the lower B channels. Compare especially the relations between neck, shoulders, arms, trunk, and legs. A child's channel is thus a designation of relative body build or robusticity.

The striking physical differences between the members of this group are, for practical purposes, entirely due to differences in body build alone, since each child has reached an equal or an almost equal level of development in exactly the same length of time. By portraying this group according to their Grid positions, one can recognize distinctive physical features that should be looked for and studied during the physical examination. Rotundity of body contours contrasts with increasing grades of angularity. The stocky solid features of the A_2 channel children gradually but definitely pass over into the more and more slender types in B_1 and B_2 to become nearly extreme in B_4 and beyond. Moreover, stockiness in one part of the body corresponds to a kind of proportionate stockiness in another part. To be sure, these children are

not of the same height and weight, and the differences to be seen among them are not simply a matter of height or of weight alone. Indeed, the photograph shows clearly that certain *combinations* of height and weight produce certain characteristic contours that define specifically different body types, measurable on the Grid by the different channel classes from A_4 and above to B_4 and below. Theoretically, the gradation is no doubt a continuous one, but for practical purposes the width of each channel is such that clear distinctions can be made out between children in adjacent channels. The girls in B_1, for example, are only slightly but quite definitely of a stockier build than their developmental peers in B_2. Inspection of the face, neck, shoulders, arms, thighs, and legs leaves no reasonable doubt on this point, and the photographic evidence is sound because care has been taken to reduce the effects of perspective to a minimum.

In this connection it is important to remember that channel widths on the Grid have been determined[1] on a basis entirely independent of any method for measuring body build or of having anything primarily to do with build per se. Channel widths have been set simply by the angular deviations within which healthy children tend to progress. Their channel once established, usually between 6 and 7 years of age, healthy children will maintain the same direction of advance within the remarkably small range of variation allowed for by channel width. This is plainly excellent sailing. In a group of 116 boys in the Harvard Series,[5] each of whom originally set out and thereafter continuously remained in the M channel for at least ten years, the standard deviation for the direction of progress turned out to be only 0.73° or 44′ of arc. This tendency to travel channelwise and thereby to maintain physique constant is an outstanding and most important characteristic of growth and development which can be independently checked in the case of any healthy child. The results will show standard deviations not significantly greater than the remarkably small value given above. One advantage of the Grid technique is that the implications of this rule of development at constant physique can be easily tested, checked, followed, and evaluated, not only for the individual child, but also for groups of children throughout the range of development.

The significance of body type is thus given an objective place in the problem of physical appraisal. A natural A_2, M, B_2, or even B_3 will be expected to remain so independently of whether every other child in the neighborhod is an M or not. Obviously one function or purpose of appraisal must therefore be to determine a child's natural channel and thereupon to advise whatever is necessary to keep him in it. The boy in Fig. 2 has no business over in the center M channel or in any other than A_2, and he will not get elsewhere if conditions of life are favorable. The girls in B_1 have returned to their own channel, but the other girls had not, at the time the picture was taken. Subsequently, however, each of

the latter three improved physical status to bring physique back to par by proceeding into B_1, B_2 and B_2-B_3* channels, respectively. These problems have been discussed more fully in the paper on simple malnutrition.[3] Here it is necessary only to note (1) that physique varies from channel to channel, (2) that the order from left to right is one of increasing slenderness, and (3) that each channel class represents differences that can be recognized by close physical inspection. Further, the admixture of physique with other components that characterize a child certainly complicates the problem of assessing physique alone by any subjective means but certainly not of doing so within the brief moment that is required to note the same child's channel position as it is plotted on a Grid and to compare the result with what is seen on direct inspection.

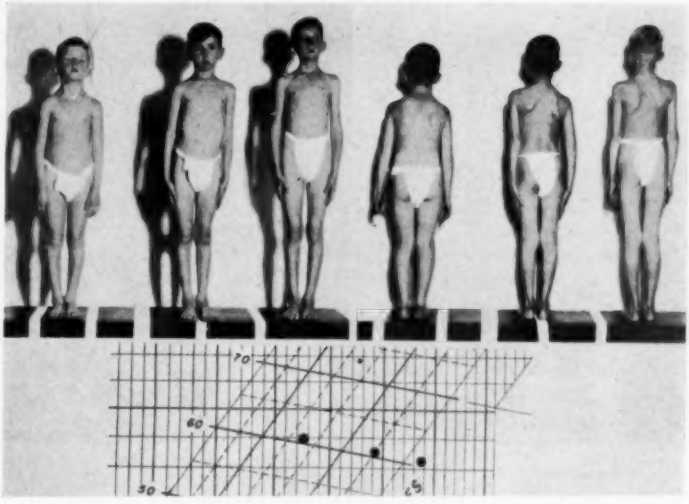

Fig. 3.—Close-up study of body build in three boys at level 61, from left to right in M, B_2-B_3, and B_4. Rotundity, smoothness, and depth of contours of the boy in M, though not so "strong" or impressive as those of the boy in A_2 (Fig. 2), are nevertheless clearly different from the increasing angularity, rippling, and thinness of body type of subjects in B_2 and below.

The important physical features that combine to produce physique as apart from the other components of physical status may be studied at even closer range in Fig. 3. Body bulk and robusticity again diminish from left to right as channel position changes from M to B_4. The differences are once more accountable to differences in physique because each of the boys has reached the same developmental level (61). To be sure, more ribs are seen in the B_4 boy than in either of the other two; and more of the outlines of the scapulae can likewise be made out in him. But the relevant feature is that he has longer and narrower lines and

*The B_3-B_4 girl in Fig. 2 is M. S. whose onset and recovery from simple malnutrition have been shown as curve 3 in Fig. 2 of paper II of this series.[3]

is suggestively more rectangular in shape than the boy in *M* whose extra bulk is, in part, made up of "better nutrition" but also of a stockier though still medium type of body frame.

Though the total range of variation in the subjects of Figs. 2 and 3 is confined within the comparatively narrow limits included between channels A_2 and B_4, which nevertheless allows for seven discrete ratings of physique that can be easily recognized, it is also of interest to study

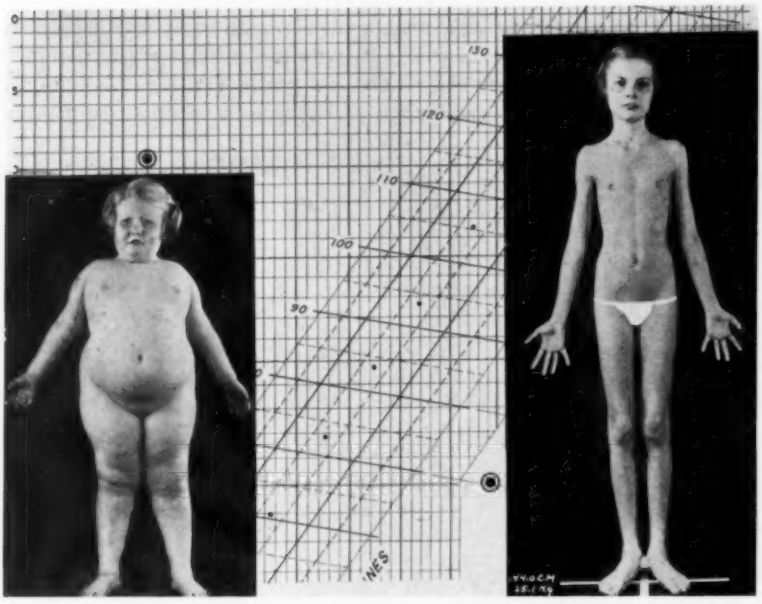

Fig. 4.—Extremes of body build represented by positions at level 107 in A_{14} and level 71 in B_7. The photographs are standardized for height.

the extreme range of variation illustrated by the two photographs in Fig. 4. The barrel-shaped rotundity of the obese girl in channel A_{14} at level 107 contrasts strikingly with the extreme "Jack-in-the-beanstalk" sliver type displayed by the girl in B_7 at level 80. From all the foregoing illustrations it is thus evident how physique may be identified, measured, and denoted simply by reading the particular channel into which a child's height-weight point falls.

Significance of Development

In a fashion somewhat similar to that just now employed to illustrate the meaning of physique, one can also portray the fundamental significance of development and its unit in the Grid system, developmental level. In this case (Fig. 5) a group of children are chosen who represent different positions or levels in the same channel, neglecting for the

moment any consideration as to whether a child is in the channel by virtue of having always traveled channelwise or by having moved into it either from above or below. There is also a reservation concerning age which must be made. Ordinarily children at the higher levels will be older than those at lower levels. But it is quite possible to select an actual group in which the reverse or almost any desired combination of age and level might exist.

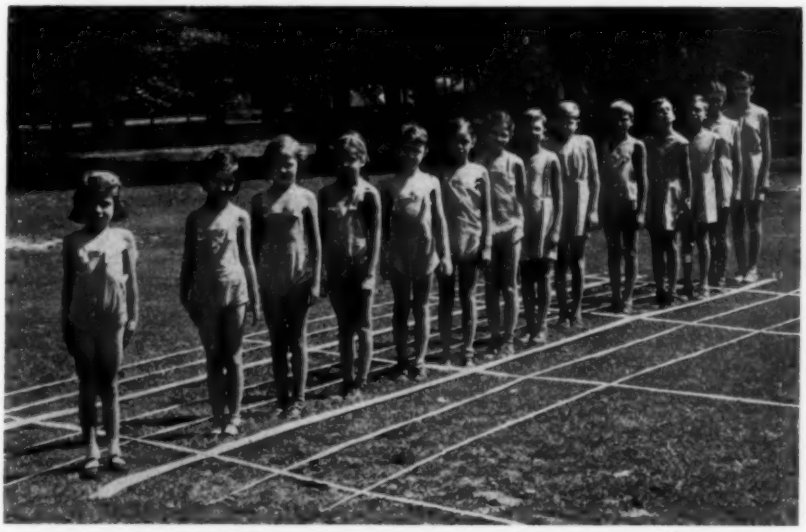

Fig. 5.—Differences between children in the same channel as here, for example, in B_1, correspond to differences in developmental level. Note how each child save one conforms to the same body type. The exception is the sixth from the right, a boy whose natural channel is A_2 but who has drifted over into B_1 as the result of bilateral bronchiectasis. The children in the foreground are smaller "editions" of those at the higher levels. Physical differences between members of this group, unlike those in Figs. 2 and 3, have nothing to do with differences in physique and, neglecting nutritional grade, can be accounted for by differences in level alone, since body build is the same.

For the present it is sufficient to choose simply the handiest group so arranged that succeeding positions correspond to successively higher levels. The first and smallest girl in Fig. 5 is at level 29, the last and tallest at level 138, the children in between being scattered at irregular intervals. By comparison with Fig. 2 one can recognize the two girls near the center and thus identify levels 78 and 79, respectively. The picture is somewhat diagrammatic because, owing to matters of focus and perspective, the children could not be spaced to a uniform scale.

Fig. 5 shows two important results; namely, (1) that body build or physique for children in the *same* channel is essentially the same, irrespective of level, and (2) that increasing level in the same channel corresponds to increase in size without significant change in physique. Casual inspection of this illustration clearly reveals the quite obvious

relation between size and level; close study, however, will also demonstrate how similar in build these different children are in spite of the great differences in size between the first and last. Again, the shape and relations of head, neck, and shoulders, the contours of thorax and hip, as well as those of thighs and legs, are similar from child to child, and this similarity is almost more perceptible to the eye than it could be made by a set of figures defining the shape of various parts of the body. Only one child in the line-up seems out of place, the sixth from the right—a boy who happened at the time to have slipped over from his natural A_2 channel into this B_1 group, owing to the effects of chronic bilateral bronchiectasis. With this exception, purposely introduced, the remaining children conform to one type and one physical pattern.

The foregoing results suggest an interesting analogy between the physical characteristics of physique and development in children on the one hand and the distinguishing features of various kinds of printer's type on the other, for if type style would correspond to physique, type size would correspond to development. Thus the strong and impressive features of Goudy Forum might, for example, compare with the physique represented by channel A_2 in which typical athletes are found; whereas the long, slender, and light lines of Lightface Gothic would compare with the thin varieties of physique in the lower B channels. But just as each font has varying sizes from 4 point to 48 point, so, too, are there children of each physique at lower and higher levels of development. And, finally, if one wishes to compare type of different style or pattern, one would most advantageously do so by comparing examples representing the same point size.* Similarly, in the case of physique, one can get a truer understanding of the basic differences between various types of body build if comparisons are made as in Figs. 2 and 3 of children at the same developmental levels.

Combinations of Physique and Development.—From what has been said, it is evident that no complete analysis or estimate of physical condition can be made without specific attention to the separate effects produced by the attributes of physique and developmental level in the ultimate make-up of an individual child. These separate effects have been discussed in the foregoing section by comparing (1) children of *different* physiques at the *same* developmental level and conversely (2) children of the *same* physique (i.e., the *same* channel) at widely different levels. In this way it has been possible to see how each of these two important attributes enter into the problem of physical condition and also how

*For example:

	STYLE (ANALOGOUS TO BODY BUILD)		
	GOUDY	LIGHTFACE GOTHIC	
Size (Analogous to Developmental Level)	PHYSIQUE	PHYSIQUE	12 pt.
	PHYSIQUE	PHYSIQUE	8 pt.

each may be easily identified and measured by means of the Grid technique through graphic resolution of heights and weights into channel and level components.

Now, since physique and development always enter into some particular combination simultaneously, it is also necessary to see to what extent different *combinations* of body type and developmental level contribute to a child's physical condition. This is an even more difficult matter when it is attacked by ordinary clinical methods, but its proper evaluation is a sine qua non of physical appraisal. By the Grid technique, however, it is simply the next logical step in appraisal, whether it involves groups or only individual children. It will be seen, moreover, that a study of particular combinations of physique and developmental level now approaches what amounts to an investigation of the compound attribute *physical status* itself. Indeed, to complete the assessment of physical status, all that is lacking is a knowledge of nutritional grade, which will be discussed in a later section.

Fig. 6.—A two-dimensional arrangement of the group originally shown in Fig. 1, to illustrate the effect of various *combinations* of physique and development represented by positions at different levels in the several channels. The problem of screening is solved by selecting out the four children on the right in B_2 and B_3 for intensive study and check-up. Physical status in the remaining six is presumptively "good," since they occupy positions in one of the three center channels, and these subjects would accordingly require no more than a "quick inspection" for tonsils, carious teeth, or other minor physical defects. Note the orderly gradation across as well as along channels in accordance with differences in physique and in level.

The problem of studying various combinations of physique and development is illustrated by the effects obtained when the children originally grouped in Fig. 1 are redistributed in accordance with their Grid positions to form the two-dimensional spatial array portrayed in Fig. 6. By this simple rearrangement the apparent heterogeneity of Fig. 1 becomes transformed into a systematic homogeneity and orderliness in Fig. 6. Here physique and development are oriented and each varies

independently along its own axis. The all but hopeless mixture of tall and short, thick and thin in the former photograph is disentangled in the latter, because the fundamental attributes—physique and level of development—are made use of and put to work, with the result that their various combinations can be more readily understood, visualized, and subsequently dealt with for the purposes of appraisal.

Six of the original group are distributed in the three center channels; three children are in A_1 at levels 94 and 102; two are in M at 99 and 105; one is at 99 in B_1; three are in B_2 at 99, 100, and 110, and one is in B_4 at 94. One "flew the coop" between exposures for Figs. 1 and 6. She is the little dark-haired girl (second from right in Fig. 1) who would have been placed at 88 in B_2.

The six children in the center channels, A_1, M, and B_1, are, according to the usual rule, to be considered of "good" physical status; those in B_2 are "borderline" and the boy in B_4 at the extreme lower right is "poor."

For certain restricted purposes, only this much information is sought or desired as, for example, in quick surveys, and for these purposes no simpler or more reliable method of "screening" groups of children is available than is offered by the Grid technique.* The example illustrated in Figs. 1 and 6 shows how readily children in unfavorable positions can be selected and then referred without delay for more extensive investigation. It is generally accepted that 30 per cent of children require close medical supervision and follow-up. The baffling question, however, has always been just which of a given group fall into the class that needs attention. Clinical methods supported by laboratory tests and various other means[1] have shown no more than about 60 per cent over-all success in this vital problem of selection. The hazards and difficulties in the problem, as represented by the random grouping of Fig. 1, are completely eliminated and solved by the orderly array and distribution in Fig. 6 which depend solely on due recognition of the important attributes of physique and developmental level as they help to determine but *do not completely define* a child's physical status.

Apart from the practical ease of "screening" a group of children or of having the results independent of personal bias or even of error, the two-dimensional orientation of Fig. 6 illustrates clearly the otherwise almost insuperable difficulty of rendering a uniformly comparable assessment of children of different physiques, different levels, and different combinations of these two physical attributes.

Physical Status Not Independent of Channel Level.—Without some special study, it might at first appear as though the compound attribute *physical status* could be determined solely on the basis of the channel a child is in at a given moment. For example, a boy or girl in B_2 is con-

*A more complete method of screening would also involve assessment of progress, especially the matter of retardation.

sidered fair, irrespective of his or her level in B_2. This would seem to imply that physical status depends only on physique but not on developmental level and hence might even lead to the erroneous conclusion that physique and physical status are really identical affairs.

A brief consideration of this possible misunderstanding is worth while, not only on its own account, but chiefly because it will help to illustrate the part which development per se, as expressed in level lines, contributes to the more complicated item of physical status.

From the clinical side of the problem of appraisal it would certainly be difficult, if not impossible, to accept the idea that development does not contribute to what is meant by physical status. It is, in fact, precisely this impossibility of rejecting a close connection between a child's physical status and his development that causes considerable initial difficulty in reconciling the apparent paradox that physical status should, on the one hand, depend somehow on development and yet appear not to do so if a child is always to be considered fair, irrespective of whether he is at high, middle, or low levels in the B_2 channel.

A very simple explanation of these difficulties can be given and, what is even more important, convincing proof can also be brought forward that physical status does depend, among other things, on developmental level by mere rearrangement of the same group of children who appear in Figs. 1 and 6.

Assume, for the moment, that physical status is determined only by channel and not by level. This would mean that physical status is independent of developmental level and hence that physique and physical status were merely two names for the same thing. Now, if this were true, and if children of different channels and of different levels were deliberately placed at the same level, they should, accordingly, show just as regular a gradation from channel to channel as that displayed by the children in Fig. 2 who are actually at the same developmental level. In contradistinction, however, the photograph in Fig. 7 shows an unevenness and irregularity *between* as well as *within* channels that have been caused solely by placing children who are actually at different levels upon the same level. This irregularity is clearly distinguishable from the even gradation from channel to channel that is portrayed by the isodevelopmental children in Fig. 2. Since this unevenness can again be removed simply by re-establishing the more or less proportionate spacings in Fig. 6 and thus by allowing for differences in level, it is clear that the jagged effects in Fig. 7 are, in a sense, an indication of the part which differences in development contribute to status at different levels in a given channel.

Going back to the analogy with printer's type, one gains an impression of irregularity in Fig. 7 quite similar to that conveyed by a page printed indiscriminately in large and small sizes of type of different fonts.

The striking irregularities that are evident in Fig. 7 from channel to channel, which are caused solely by the differences between children in the same channel,* conclusively demonstrate, first, that some property of each child, call it X, depends not only on his physique, but also on his developmental level; and, second, that an attempt to "flatten" or compress X, which is at least a two-dimensional affair, into a one-dimensional array, artificially distorts the facts and confuses the true relations between physique, developmental level, and property X.

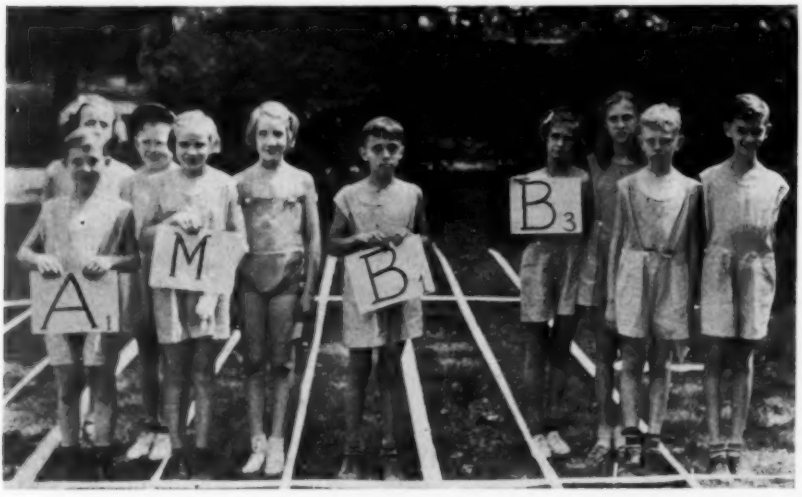

Fig. 7.—The subjects of Fig. 6, arrayed by channel, *i.e.*, by physique, but placed on the same level to show the effect of neglecting the component of development. The uniform pattern of Fig. 6 is now lost except for differences in physique as represented by subjects in different channels. Children within the same channel differ physically in that they have actually attained the various levels allowed for in Fig. 6. Taken together, Figs. 6 and 7 show how two of three components of physical status help to define that attribute.

What is more natural, then, especially from the clinical point of view, than to identify this property X with what is accepted to be a child's physical status; if this be done, physical status clearly depends on physique and developmental level taken together and not upon body build alone. Two questions remain: (1) How, then, if physical status is not the same from level to level in a given channel, can one be satisfied to describe it at every level in a channel by only one word, such as "good," "fair," "borderline," "obese," or "poor"? And (2) what other attributes are required in order to define physical status for the purposes of assessment?

The answer to the first of these questions is now plain, for it is easy to see that such one-word descriptions apply only to the over-all estimate of physical status, and thus merely describe the *qualitative* aspect of

*Since an even gradation is obtained as in Fig. 2 by comparing children who are on the same level.

physical status that is common to children of different levels in the same channel. Such a one-word description has distinct clinical worth and is sufficient for many ordinary purposes of assessment. But no one-word qualitative description, such as "fair," should be understood to specify a child's physical status completely! For there are other matters that enter into this much more complicated attribute.

As for the second of the foregoing questions, it may be said that an indefinite number of items might actually be listed as contributing to the make-up of a given physical state. Some selection is obviously required, and, fortunately, the problem is not so hopeless as it might seem. For the purposes of Grid analysis, information on only one other attribute is necessary, and that attribute is a child's nutritional grade.

Significance of Nutritional Grade

The term nutritional grade as it is used in the Grid technique of assessing physical condition refers to the inclination of a child's curve in the channel system either with respect to the two-channel axes representing physique and developmental level or equally well with reference to the original perpendicular axes scaled in heights and weights. There are three chief varieties characterized by their direction as follows: (1) up-channel or "optimal" nutritional grade; (2) cross-channel bearing right and downward at an inclination less than that of the channel system, and indicating relative "undernutrition"; and (3) cross-channel bearing left and upward, with inclination greater than the slope of the channels and signifying, accordingly, relative "overnutrition."

A child pursuing an up-channel course develops without change of physique. This is the rule in health. It has been established by observations on many individual children,[1] and it has also been corroborated by the evidence that children who persist in developing at inclinations greater or less than the channel system ultimately become obese or undernourished, respectively, and, conversely, that the cure of undernutrition or of obesity is characterized by a reversal of the original trends.[3] Silhouettes to illustrate some of these results have been reported in the original description of the Grid technique.[1]

Another very striking example is seen in Fig. 8 which shows the before-and-after effect of six months of treatment in a convalescent hospital for severe undernutrition in a girl of 7 years of age. Full recovery has obviously taken place. The changes which the two photographs portray correspond to the change from level 45 in B_3 to level 68 in M. The total change is thus made up of a two-and-one-half-channel increase in physique *coupled with* 23 units of developmental advance, with the result that the path traversed between initial and final positions has a slope almost exactly four times the optimal value given by the channel system itself. One is thus required to distinguish carefully between a child who is actually overnourished and one who, like the

child in this example, is by no means overnourished even though her nutritional grade, for the time being, had a value much greater than the optimal value of a healthy child traveling channelwise. Thus the significance of high or low nutritional grade is to be taken only in relation to the original conditions. The fundamental meaning is simply that departures from the optimal channel slope will, if sufficiently prolonged, ultimately lead to actual states of over- or undernutrition as the clinician commonly understands these terms.

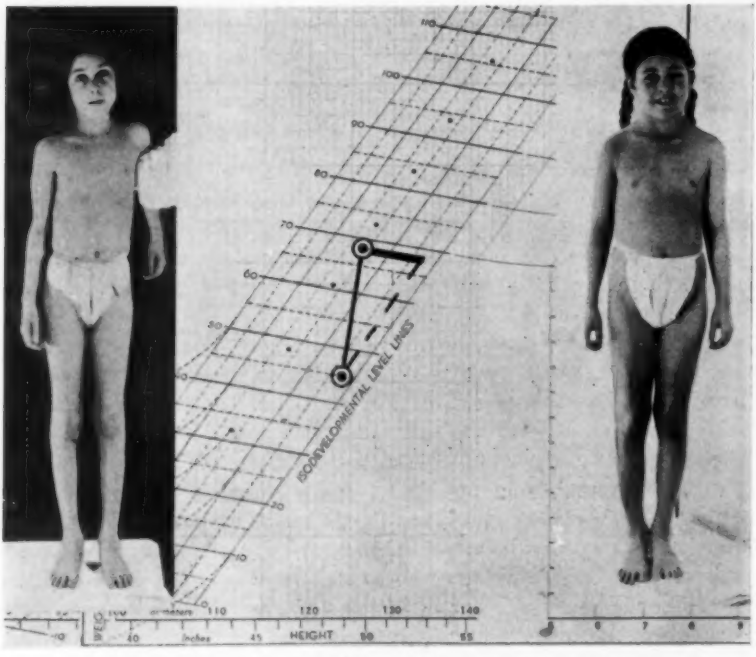

Fig. 8.—Before-and-after views of a 7-year-old girl (B. B., Rainbow Hospital No. 4470), showing the improvement of physical status in six months represented by the change in Grid position from B_3 at level 45 to M at level 68. The gradient of this path is therefore considerably higher than the optimal value represented by the inclination of the channel system. Such a gradient, much longer continued, would obviously lead to obesity. The components of recovery from simple malnutrition have been discussed at length in another paper.[3]

Just as it has been possible to portray the meaning of physique and developmental level by suitable photographic arrangement of different children, so also is it possible, as Fig. 8 shows, to illustrate nutritional grade by means of successive pictures of the same child. The actual result, to be sure, is indirectly obtained because the photographs in reality show only the resultant change which has taken place along her actual path of development, though this may be resolved by the Grid into the two contributing components, change in physique and change in level.

Nutritional Grade at an Arbitrary Point.—From what has already been said, it is clear that information on nutritional grade helps to round out an estimate of physical status that would otherwise rest, so far as the Grid method is concerned, simply upon knowledge of physique and developmental level. The fact of the matter is that knowledge of a child's nutritional grade at every point can do much more than "round out" a Grid rating of physical status; for, taken in conjunction with physique and level, a particular value of nutritional grade clinches the problem because physical status is then as completely defined as it is possible to do by this graphic method.

Consider, for example, two boys, P. and Q., at level 100 in channel B_1. Presumptively, according to the general rule, both boys are of good physical status. If nothing else is known about them at the time, there is simply no possibility of deciding whether they are or are not proceeding at the same nutritional grade. To this extent, an estimate of physical status is incomplete, though not entirely without value, for it is known that "most" boys in B_1 are sufficiently well nourished to "pass" appraisal by any method.* Such an estimate must therefore remain incomplete until (*a*) past records are obtained, or, if this is impossible, (*b*) sufficient time elapses for a second observation to be made from which the directions of the path may be reckoned. Technically, of course, neither of these would give the value of nutritional grade *at the original position;* the results would only indicate the average value for the path *between* the first and second observations. Nevertheless, a value for any arbitrarily chosen point on the path would be available and the Grid rating of physical status, with channel and level already established, would be completed.

Suppose, then, that both boys had proceeded strictly up channel, say for five levels. Their Grid ratings of physical status would therefore be the same; their ratings of progress, however, would depend on whether they had advanced at the same or at different time rates.

But suppose, lastly, that boy P. had reached level 100 in B_1 by a path leading from A_1-90, whereas boy Q. had reached the same level (B_1-100) by coming up from B_2-90, or, in general, by different modes of approach to the same point. In every case, physical status at B_1-100 would be quantitatively different, since nutritional grade had also been different.

Thus, the existence of nutritional grade at an arbitrary point is one thing, but the determination of its value at that point is quite another. Since there is no independent way to measure nutritional grade, it is always necessary to have at least a second observation either before or succeeding the point in question. Time, as it were, must be allowed to have drawn or to draw out a path, the inclination of which at once decides the issue.

*For the exceptional case see paper II[2] of this series.

But time itself does not enter the forefront of the problem of status, for it belongs rather to the question of progress which, in turn, may be viewed simply as the result of passing physical states. The problem of status is thus merely a first step toward the solution of the more general and on the whole more significant as well as more important problem of progress.

To evaluate status we must first fix upon its three components, physique, developmental level, and nutritional grade. To evaluate progress we need only note how sequential states behave with the passing of time.

Consideration of time as an additional variable enormously increases the variety of possible combinations among the four principal attributes when it is recalled that the range of each is also great. Such wide variety must be expected in order to conform in detail with the correspondingly great differences among children that come within the sphere of appraisal. Counting only nine channels with 180 levels and three main paths of change, one finds almost 5,000 individually recognizable states among children from 2 to 18 years of age. Since at least half of these could occur at any age between 7 and 15 years and could be further characterized by whether progress is on or ahead of any one of twelve schedules and at, below, or above par, one faces the task of attempting to deal with even more than 2,500 by 8 by 12 by 3, or from 750,000 to one million different but quite possible varieties of physical condition. To which of these does Johnny belong when he comes up for appraisal?

This problem clearly demands systematic handling. The first step to evaluate physical status is achieved for every height-weight point by simply expressing a child's Grid position in terms of his physique, developmental level, and nutritional grade. The next step logically involves the study of an aggregate of physical states linked by the common thread of time and thus leads to an evaluation of physical progress.

Having now seen how heights and weights are combined to give physique, development, and nutritional grade, and how these in turn are combined again to give physical status, it is interesting to study some of the important differences that may actually be found among children who happen to have the same height. An example of how greatly both physique and development may differ in this circumstance is shown in Fig. 9. These six children though of the same height (54 to 54½ inches) show the following differences (from left to right in the figure):

PHYSIQUE	DEVELOPMENTAL LEVEL
B_5-B_4	76
B_4	90
B_3	91
B_3	93
A_1-M	101
A_1	102

A similar result would also be obtained if one chose to compare differences that commonly exist between children of the same weight. In this case, however, as can be seen from a Grid, the range of development is not as great as in the foregoing example, and the actual physical differences between children of the same weight are therefore almost wholly due to differences in physique.

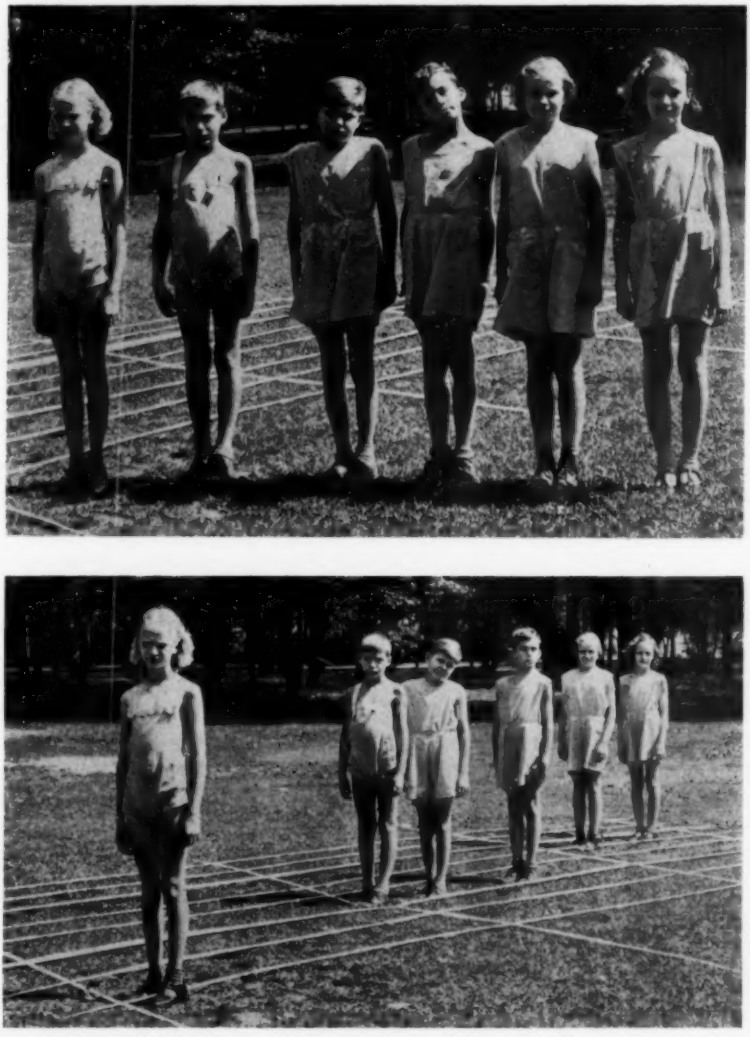

Fig. 9.—Showing how children of the same height (54 to 54½ inches) may actually differ widely not only in physique, but also in development. The significance of these fundamental differences from the clinical standpoint of appraisal and from the physiologic standpoint of differences in metabolism is discussed in the text.

These results are important not only from the standpoint of the problem of appraising the physical condition of children but also, as already emphasized,[1] for the physiologic problems connected with estimates of basal heat production.

From the former point of view (appraisal), it is clear (1) that an assessment of physical condition based on measurements that give height alone must be very precarious and (2) that although children of the same height may have the same physique (in which case they would also have the same weight and would therefore also be at the same developmental level), it is more usual to find that they differ widely not only in physique but also in development.

From the standpoint of metabolism, it may be recalled that basal heat production is independent of physique and that it may be estimated from developmental level alone.[1] Thus the children in Fig. 9 could not be expected to have the same metabolism and this would be so not because they are of different physique but only because they have reached different developmental levels, although they are equally tall. These relationships whereby greater differences in level are to be found among children of equal heights than among those of equal weights explain why the variation of metabolism based on height is always greater* than that based on weight[6] and also why the former estimates require about two and one-half times the correction of estimates that are made on the basis of weight.[7] Taken together, these results clearly point to some of the more intriguing connections between the components of physical status on the one hand and the fundamental physiologic matters of metabolism on the other; and the existence of such connections provides an even sounder basis than otherwise for the purposes of physical appraisal.

II. THE EVALUATION OF PHYSICAL PROGRESS

The fundamental issue here is to solve the problem of differentiating objectively between children whose progress has been and is satisfactory from those in whom it has not been so. Although two quite different situations arise in practice, namely, the solution of this question among groups of children to decide which is which, and also the evaluation of progress in a given child, it is worth noting that the principles and method of appraisal are identical. In either case a child is to be judged in terms of what he himself is accomplishing in the way of growth,

*In spite of the well-known fact that the variability of height itself is generally two to three and even four times less than that of weight. The curious paradox whereby mean values for metabolism are more uncertain when children are grouped according to their less variable heights than according to their more variable weights is generally overlooked, though it has great significance in the important problem of establishing satisfactory and precise standards of basal heat production. But, as suggested briefly in the text, this paradox is completely reconciled in the Grid technique through the combination of four basic facts: (1) the relation of heights and weights to physique and development; (2) the independence of physique and metabolism; (3) the consequent high correlation between developmental level and metabolism; and, finally, (4) the greater range of development (within equal limits of physique) when height is fixed than when weight is constant. Had the foregoing anomalous results been unknown, they could thus have been predicted; the explanation of their existence, accordingly, constitutes a rigorous test of the validity of Grid estimates of metabolism.

development, and physical progress, not primarily as compared with others but first and foremost as compared with what he, with his equipment and with his settings, had started out to do. This, clearly, is applying the principle of *each child his own standard of comparison* to the full.

Until now, attention has been centered on the three components which determine physical status. For a given position in the channel system a number of different physical states are possible, owing to the fact that the developmental path through any position may have one of several values. Two different positions will always determine different physical states, and if a child has passed from one to another position, the difference can, in general, be recognized and estimated. But comparing two physical states, like comparing two still pictures, does not suffice to determine progress. To do this, one needs, in addition, to consider the important role of time, for the essence of progress is the time sequence between physical states, and this involves not only elapsed time itself, but also the indirect effects that have to do with the time rates at which physique, development, and nutritional grade, and hence physical status, are undergoing the changes visible at the end points of a path or of a path segment.

Mixed up with time per se is the capricious question of age. Much of the difficulty and confusion in the problem of rendering physical appraisals on children is caused solely by wide misunderstanding as to the proper roles which age and time represent. Both of these variables will be considered in order to show how time and age enter most significantly into the problem of assessing physical condition.

Defects in Classifying Children by Age.—Wherever groups of children are dealt with, whether for purposes of child health survey or for studies on growth, it is customary, in summarizing reports, to classify the groups according to age. No better example to demonstrate how such a procedure is actually destined to suppress rather than to reveal significant relations could possibly be given than the routine custom of placing children in age groups. Yet it is still practiced today, as is evident from reports in the latest journals, leaflets, and monographs.

Classifying children by age, though one of the chief defects in ordinary height-weight-age tables, has received scarcely any critical study even by those who object to the use of the tables but who, in turn, report and compare results on an age basis. Now, grouping children according to age, however valuable for the purposes of a census, is bound to obliterate almost completely the real effects of growth and development that characterize the individual members or even the group as a whole. It is illuminating and exceedingly worth while to see how seriously the failure to recognize this defect has actually hampered rather than helped the practical problem of assessing physical fitness among children.

Consider, for example, what is bound to happen in any group of, say, "10-year-olds." A glance at the auxodrome panel of a Grid (Fig. 10)* shows that children of 10 years may be found at any or every level of development between 50 and 135, 96 per cent of these being expected between levels 61 and 118. But, turning to the Grid panel proper, it will be seen that the 85 levels from 50 to 135, and the nine regular channels A_4 to B_4, inclusive, which comprise practically one-half the entire field, provide for considerable difference in body build and development even in children of the *same* age (10). If levels were grouped in fives, say, one must be prepared to find at least 153 (17 by 9) distinguishably different varieties and combinations of build and development alone, disregarding entirely the effect of nutritional grade. The actual total, however, would more likely exceed 1,200 separate combinations, by virtue of the appearance of some children in positions outside A_4 and B_4, and also because discrimination by individual levels is not at all impossible.

Suppose, now, a thousand such children gathered for inspection on the school grounds. Would an observer, if asked to estimate their age, be likely to answer "10 years" for all of them? Without question, no. Instead, his assessments would range from 7 to 14 years, at least, because he would be led subconsciously to render his judgments in terms of the age each child *appeared* to represent, which, therefore, would really be a kind of developmental age. A spread of seven years is, in fact, about the range of "developmental age" to be expected among 10-year-old children, as may be seen on a Grid by reading the ages at which the 67 per cent standard auxodrome crosses levels 50 and 135, respectively.†

What makes the matter still more confusing where primary classification by age is practiced, though it accounts nicely for the commonly heard remark about the infinite variety among children, is the fact that for a number of years on either side of 10 a very considerable amount of overlapping occurs in the channel system. Thus, in a survey of 8- to 12-year-old children, for example, there will be many in each age group whose physique and developmental level are precisely the same as the body build and level of children in every other age group. One must expect, therefore, to find at any age children of any physique, of almost any level, and of any nutritional grade. This is thorough "mixing," and it will complicate analysis as long as age grouping is insisted upon.

An outstanding characteristic of data on height and weight plotted against age is that they scatter "all over the map." But this is precisely what one must expect from the foregoing discussion on varieties among 10-year-olds. The same results, applied to other ages, fully demonstrate why correlations of various body traits with respect to age have tradi-

*See also Fig. 1 in paper I.[3]

†Entirely similar statements apply to other ages. A better understanding of the significance which must be attached to the great range in developmental level that may be expected at any age can be gained from a study of the two 12-year-old boys and their Grid positions in Fig. 10.

tionally been inexplicably low. They account also for the wide dispersions and the broad zones that are sometimes ascribed to individual variation. Actually, however, such zones have been distended by the artificial aggregation of subjects whose only common attributes are life and age. Few results, moreover, that possess this ever-recurring wide range of variation about age means can possibly serve any useful purpose. Averages thus encumbered throw no new light on the problem; they hide essential facts by their broadly flung cloaks of variation, but what is still worse, they even lead to the mistaken and wholly unjustified conclusion that measurements themselves have little or no worth! One might, with more logic, draw the conclusion that age plays no recognizable part in growth and development or in the immediate problem of assessing the physical condition of children were it not for the forbidding general rule that children grow taller, become heavier, and change in other respects as they grow older.

The point which must be clearly emphasized is simply this: Age and time are very important factors, but neither of them is permitted, through the usual manipulations of age selection, to show or to play its own unique and indispensable role in connection with those matters of growth and development that are vital to the problem of assessing physical condition.

The Role of Time.—Aside from being the universal leveler, time enters specifically into the phenomenon of physical progress. It is through time that one physical state passes into another. The lapse of equal amounts of time often produces quite different responses in growing and developing children, even though other conditions might be nearly the same. These differences might be everyday events and perfectly normal, or, again, they might not be consistent with health. For example, the two years between the ages of 3 and 5 are characterized chiefly by a process that changes the chubby infant into a slender child. The direction of development is here normally across channels, bearing right at an inclination that could never thereafter be anything but pathologic unless deliberately induced. The slope of this segment, in fact, reaches a minimum value of about 1.1, which is therefore only 39 per cent of the channel pitch in later years. Yet the annual rate of advance is comparatively high, 10 units in twelve months or 83 per cent of the average rate for the next ten years.

The dynamic connections of time with the processes and events of growth and development afford an examiner a unique opportunity to make use of time in his assessments of physical condition. What might otherwise turn out to be a stack of isolated physical states, piled up one after another, like single snapshots or lantern slides, is transformed by time into a running sequence. By the simple expedient of measuring time and position, the examiner can at once distinguish between the child who is simply "idling" and the one who is making satisfactory progress.

Time, moreover, has its connections with age, and these, too, are subject to certain constraints. An important part of the whole problem is to define these relationships so that one may learn to what extent time itself and age, particularly, govern the main transactions of growth and development.

Fortunately, the answers to these questions are not hard to find. They are contained in and may be explained by the mechanism of the family of five curves called auxodromes or age schedules of development, which are marked out on the right-hand panel of a Grid record.

The Role of Age and Age Schedules of Development.—A simple analogy will clarify the proper role of age itself, as well as that of the auxodromes, in connection with the problem of assessing the physical condition of children.

Suppose a mother wished to learn at what time her child would arrive in town by train. She would certainly not call for information about the length of the train nor about the weight of one of the cars. She might, to be sure, simply ask about the train from New York, but as long as there were several of these she would have to give the clerk some information about the train her child is on, either number, name, or its departure, before he, in turn, could announce its expected time of arrival. Had she looked the matter up herself, she would also have proceeded first to identify the train in the schedules and then simply to read out the time of its arrival.

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This close similarity between railroad and developmental schedules may be further illustrated by Table I which is set up in the usual timetable fashion. From this the direct relations between age and time are immediately evident. Further comparisons are listed in the following tabulation of equivalents:

RAILROAD		GROWTH AND DEVELOPMENT
Timetable	corresponds to	Timetable
Train number	corresponds to	Auxodrome number
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It will be seen that train name or number, as a mark of identification, corresponds to the percentile figure attached to each auxodrome which represents the fraction of children in the general population who may be expected to have reached successive levels at or before the indicated ages. Thus, for example, only 2 per cent of children will have reached

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	DEVELOPMENTAL LEVEL	AUXODROME, OR SCHEDULE OF DEVELOPMENT				
		2• (YR.)	15• (YR.)	67• (YR.)	82• (YR.)	98• (YR.)
Lv.	0	----	----	2.8	----	-----
Ar.	10	----	----	3.8	----	-----
Ar.	20	----	----	4.9	----	-----
Ar.	25	----	----	----	----	6.8
Ar.	30	----	----	5.8	7.1	7.25
Ar.	35	----	----	----	7.3	7.7
Ar.	40	----	----	6.5	7.6	8.1
Ar.	45	----	----	----	8.0	8.4
Ar.	50	----	6.2	7.2	8.4	8.85
Ar.	55	5.1	----	----	8.8	9.35
Ar.	60	5.5	6.8	7.8	9.2	9.80
Ar.	65	----	----	----	9.7	10.35
Ar.	70	6.2	7.6	8.75	10.05	10.90
Ar.	75	----	----	----	10.5	-----
Ar.	80	6.8	8.4	9.7	10.9	-----
Ar.	85	----	----	----	11.4	-----
Ar.	90	7.6	9.4	10.6	12.0	13.30
Ar.	95	----	----	----	----	-----
Ar.	100	8.3	10.25	11.6	12.9	14.20
Ar.	105	----	----	----	----	14.60
Ar.	110	9.25	11.2	12.4	13.6	-----
Ar.	115	----	----	----	----	15.25
Ar.	120	10.2	11.8	13.2	14.2	15.60
Ar.	125	----	----	----	----	-----
Ar.	130	11.0	12.6	13.6	14.8	16.10
Ar.	135	----	----	----	----	-----
Ar.	140	11.8	13.25	14.3	15.7	16.80
Ar.	145	----	----	----	16.2	17.3
Ar.	150	12.6	13.8	15.0	17.2	18.8
Ar.	155	----	----	----	----	-----
Ar.	160	13.2	14.7	16.0	----	-----
Ar.	165	----	----	----	----	-----
Ar.	170	14.0	16.0	17.5	----	-----
Ar.	175	----	----	----	----	-----
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*Girls also follow these schedules closely until the age of 9 or 10 years. For four years thereafter they tend to proceed ahead of a boy on the corresponding auxodrome by about six months and finally "turn the corner" of development at menarcheal onset, to reach somewhat lower limits of development than the corresponding boy. Thus, 52 per cent of boys may be expected to proceed on schedules between the 15 and 67 per cent standards and there to reach an average upper level of about 170, whereas an equal percentage of girls, progressing on the same schedules (*i.e.*, between the 15 and 67 per cent auxodromes) will ultimately attain no more than the 145th level of development. These results can be seen in the three-color Grid.

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level 90 as early as 7.6 years, but 67 per cent will have done so by age 10.6. Likewise, 98 per cent of children will be expected to arrive at level 65 on or before they become 10.35 years old. Arrivals at level 55 before 5 years, or after 9.35 years, are, so to speak, in "classes by themselves," the former on much earlier and the latter on much later schedules than the vast majority of children.

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clear, moreover, that any schedule, including those not specifically represented by a standard auxodrome or in Table I, could have been chosen as the schedule from which to reckon advancement or retardation. For example, the 50 per cent auxodrome, though not indicated explicitly, lies in the region between the 15 per cent and the 67 per cent schedules. Reckoning advancement and retardation from the 50 per cent auxodrome would have been just as legitimate a procedure as to employ the 67 per cent schedule for this purpose. In doing so, however, it would have had the disadvantage of suggesting that there are just as many retarded as

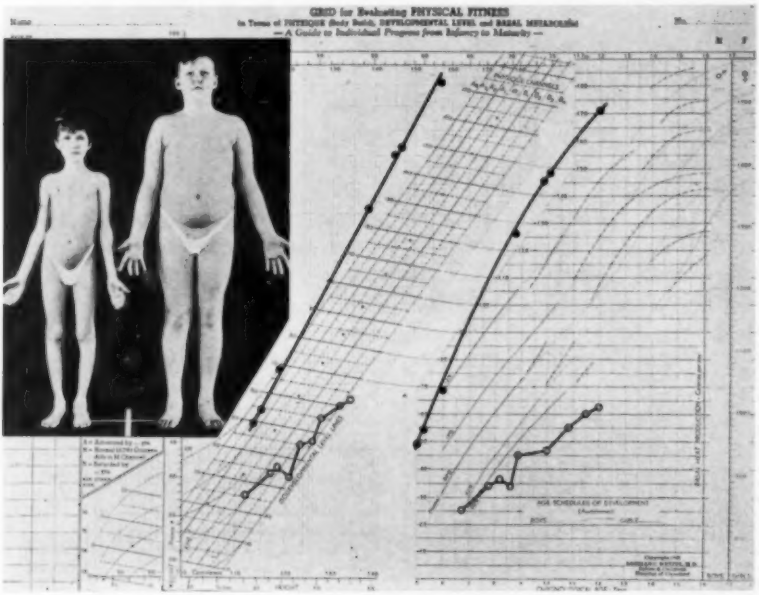

Fig. 10.—Two boys exactly 12 years old who differ in physique, development, nutritional grade, and hence in physical status, as well as in physical progress. Between them are almost countless possible variants in spite of age equality. This example illustrates graphically what is shown in Table I; namely, that knowledge of age has no value aside from that of determining specifically whether a child is "on" or "off" his schedule of development. It also explains the artificially wide dispersions that characterize age averages.

advanced children in the population. This, however, does not appear actually to be the case, though the point cannot be proved since there is no absolute standard by which advancement or retardation per se can be judged. It is much more plausible that of 100 children in the race of growth, the first sixty-seven be considered "on" or "ahead of" time and only the latter third of them retarded.

A final example, given in Fig. 10, will suffice to illustrate the mechanism and function of the auxodromes, and it will, at the same time, also show how selection and classification of children by age introduces unnecessary confusion in the problems of evaluating both physical status

and physical progress. The two boys in the figure were exactly 12 years old; the larger obese boy had reached level 171 in channel A_8, whereas the smaller, severely malnourished lad had only reached level 63 in B_4. The boys, accordingly, differed in physique as well as in development, but neither of these differences can be explained on the basis of age since one boy is just as old as the other.

The differences the boys represent must therefore be clearly due to what has been happening to them within an identical period of time, and hence specifically to fundamental differences in their physical progress which is completely defined for the purposes of appraisal when we know (*a*) the channel course and (*b*) the auxodrome by which they reached their respective levels at 12 years of age. As these curves in the figure clearly show, there never was a time during the interval of observation in which the boys were alike and for that matter could be supposed to be alike. Both boys' curves, to be sure, are abnormal, and it is readily seen to what extent and in what respect this has always been so. The one boy has advanced too rapidly, the other too slowly; the one toward obesity, the other toward undernutrition. Both boys, strictly speaking, are "failures" in growth and development; the one too much and too soon and the other too little and too late.

Considering their initial values, one would surmise that the larger lad would have been better off to have steered a course along A_2 or even along A_3 on a schedule corresponding to the 2 per cent auxodrome, whereas the smaller fellow, other things being equal, would seem to have been intended for a growth voyage in B_1 on a naturally retarded schedule in the neighborhood of the 82 per cent auxodrome. Even under these circumstances, however, they would never have been alike at any age between 5 and 12 years, though likeness is precisely what is implied when age averages of any kind are resorted to or when classification by age is practiced.

Returning, however, to the differences the boys display and to the fact that these are basically assignable to differences in channel and auxodromic progress and not to age, one can gain a still more graphic understanding of the meaning and purpose of the auxodromes from the following possibilities:

(*a*) Suppose that, instead of what happened, both boys had traveled the same channel and had done so by reaching each level at the same age. They would then have had the *same* physique, development, nutritional grade and, finally, the *same* age advancement. From the standpoint of the Grid, they would then have been substantially like identical twins. But suppose (*b*) that in traveling the same channel, they had done so according to their original schedules, the larger boy again having reached level 171 in *M*, say, and the smaller lad, level 63 in *M*. In this case physique and nutritional grade would have been the same, but development would have differed in level as 171:63. The little fellow at 63

would thus have represented simply a smaller "edition" of the other lad at 171, but this difference would again be associated with the original differences in auxodromic progress, whereby one boy was continuously accelerating ahead of a very advanced schedule (the 2 per cent auxodrome), the other continuously decelerating behind the comparatively retarded 82 per cent auxodrome. Hence, neither boy could be expected, even with physique the same, to reach equal levels of development, as long as both were initially destined to proceed on widely different schedules of advancement.

In substance, then, it will be seen (1) that since physique, like eye color, is independent of age, one cannot predict a given child's physique by knowing only his age; (2) that one cannot predict developmental level from age unless one also knows the particular auxodrome or schedule the child is supposed to be following, and, accordingly, (3) that the only value in noting age at all is to determine whether a child is "on time"; that is, progressing according to his own specific schedule or not.*

Developmental Age.—To know that a child is advanced in development is one thing; to know that he is two years advanced is much more, and this will do for certain purposes. For other purposes it is somewhat more useful to say explicitly that a child of 10 years of age has a developmental age of 12 years rather than to imply this by stating that he is two years advanced. The establishment of the 67 per cent standard auxodrome as the demarcation line between advanced and retarded children among the general population automatically makes that line the reference curve for determining "age equivalence" in development. A 10-year-old or, for that matter, a child of any age who has reached level 110 is said to have a developmental age of 12.4 years, on the basis that two-thirds of all children may be expected to have reached level 110 no later than that. While it happens that a few children will have reached level 110 as early as 8½ or 9 years,† and a few will not have done so until they are 15 or 16 years old, it is also a fact that the chances of a healthy boy reaching level 110 no later than 12.4 years are precisely two to one. The chance of the same child reaching the same level no later than 14.9 or about 15 years of age, on the one hand, is ninety-eight to two or forty-nine to one. Now, although the choice of a demarcation line is somewhat

*From the standpoint of complete and absolute finality, it may be presumed that the problem of determining a child's proper schedule is perhaps indeterminate. For practical purposes, however, one is justified in concluding that a child who is progressing at the rate of one level line per month is on his own proper schedule. Values only a little greater or less than this soon manifest recognizable departures from the standard auxodromes. In case of doubt, moreover, the "test of labor" could be made by a suitable change of environment, such as has been described in connection with the recovery phase in simple malnutrition[3] in order to determine whether the child in question will respond to that change. But nothing, obviously, is to be gained by attempting to have a child "move over" to another schedule as long as he is already progressing at the rate of a point or level line per month. Children, like watches, should run on time; and again, like clocks that keep various kinds of time, such as G. M. T., Eastern, Standard, Pacific, but each of which runs sixty minutes to the hour though each tells different local time, so should each child keep progressing one level line per month, irrespective of whether he is on an early, middle, or late schedule.

†The larger boy in Fig. 10 reached level 110 at 7.8 years. The smaller fellow seems destined never to do so. His most recent data at the age of 13 years show that he has reached level 67 in B_4.

arbitrary, but not entirely so, the two in three probability is certainly as serviceable as any other that might be chosen on either statistical or clinical grounds. Every developmental age, as determined from the age at which the 67 per cent auxodrome intersects a child's own level, thus represents on the basis of the two to one probability the child's age equivalence for that level.

Since all children on the same level have the same developmental age, it is clear that developmental age has intrinsically the same meaning as developmental level itself, though the result is expressed in years rather than in levels. One may, accordingly, specify a child as advanced or retarded by stating that he is 15 units ahead of or behind a certain standard level, or one might express the same result by giving the 67 per cent age equivalent of his level in comparison with his own age. This gives all the information that can be obtained on the point, and when the result is expressed as a developmental ratio, the various relations are immediately evident.

Developmental Ratios.—While the use of these ratios is primarily intended to afford a numerical expression of how far a child is advanced or retarded with respect to the general population, successive ratios may also be employed to indicate the character of physical progress.*

In form such a ratio is intended to show explicitly in the numerator the value of what has just been described as a child's developmental age and in the denominator his actual chronologic age. This readily enables the amount of advancement or retardation to be estimated in terms of years, a more preferable unit than the decimal fraction obtained by actual division. Two quotients, for example, might be equal, but it would be impossible to decide from the result whether the children were of the same or of different ages. Besides, the quotient of a child whose auxodrome coincides with the 15 per cent standard, for instance, would not be constant, although these two schedules (15 and 67 per cent) are everywhere close to a year apart. The quotient form actually suppresses the really significant information given by the ratio; namely, to what extent a child of given age is retarded or advanced. It is this, if anything, that would be wanted.

Maturity Ratings: Levels and Ages.—There is nothing in the definition of developmental age or in the method of determining it which could be construed to imply that equal developmental ages imply equal maturity or, more broadly, that developmental age is an unqualified measure of maturity. Failure to understand these important distinctions will lead to errors in interpretations which might prove confusing. Now, without the help of the auxodromes, neither developmental level nor developmental age gives any hint by itself as to how far a child has yet to develop. It is impossible, for example, to predict simply from the

*For a completely worked out example of how developmental ratios may be employed to measure physical progress, see Table III in paper I of this series.[3]

level of a child's point in the channel system how far beyond that level he is destined to proceed. But the moment his level is plotted in the auxodrome panel and his schedule of development thus identified, one can get an approximate indication of how far he is likely to develop because each member of the family of auxodromes has its own quite characteristic upper limit. The boy or girl who is on an advanced or early auxodrome tends ultimately to attain a higher level of development than that which children on later auxodromes ordinarily reach; hence, knowledge of a child's developmental level coupled with knowledge of his auxodrome make an estimation of the difference yet to be expected; namely, the difference between his given level and the corresponding upper limit, a matter of simple subtraction. Or, if preferred, a maturity rating can be easily computed from the same original information by expressing his actual level as a fraction or percentage of the expected upper limit of development toward which the corresponding auxodrome is approaching.

In a manner comparable to that of determining developmental age, one can also estimate maturity age. For example, take the point represented by level 110 at 10 years. The auxodrome through this point, parallel to the 2 per cent standard, runs about 0.75 year behind that standard and will consequently reach its upper limit at about level 187.5 or 188. Now 110/188 = 0.585. Hence level 110 for a child on that auxodrome is equivalent to 58.5 per cent of his expected limit of development at maturity. Thus the corresponding maturity level on the 67 per cent auxodrome is 175 by 0.585, or level 102, and the maturity age, accordingly, 11.75 years, as compared with a developmental age of 12.4 years. In this connection it may be noted that the maturity rating of level 110 on the 67 per cent auxodrome is 110/175, or 62.9 per cent, as compared with the value of 58.5 per cent in the preceding example. Thus, advanced children (those on advanced auxodromes) are somewhat less mature than their developmental peers on the standard 67 per cent schedule or, in general, than those children on any auxodrome behind their own. Furthermore, maturity age approaches developmental age as a child's auxodrome approaches the 67 per cent standard. The differences between maturity age and developmental age are considerable only in those children who are far removed from the 67 per cent standard, and they are practically negligible for that 52 per cent of children who may be expected to develop on schedules lying between the 15 per cent and the 67 per cent standard auxodromes.

COMMENT

The importance of a detailed study of the components of physical status (physique, development, nutritional grade) and of physical progress (channel course, auxodrome) is twofold. In the first place they form the foundations upon which an evaluation of growth and develop-

ment can be made either at a given point (physical status) or for sets of points (physical progress). As the chief results of this series of papers have shown, an evaluation of growth and development constitutes by far the dominant part of an appraisal of physical condition in children. Indeed, in many respects, if not in all, nothing would seem to be of greater consequence. Satisfactory growth and development, to be sure, do not eliminate the possibility of coexisting disease or of minor physical defects. On the other hand, however, unsuspected trouble may sometimes first be found because growth and development have been failing. Moreover, prognostic outlook is generally more favorable when it can be shown objectively that disease has not succeeded in impairing growth. But whatever the need or purpose of appraisal in actual practice may happen to be, whether for large scale screening or for individual assessment on an occasion of routine follow-up, a rating of physical condition will depend ultimately on the values which physique, development, nutritional grade and auxodrome turn out to have. For this reason the present study has been concerned mainly with a further inquiry into the significance which the three components of physical status possess when they are taken singly or in various combinations. From these more elementary steps it has sought also to show how the measurement and evaluation of physical progress may then be built up out of a time and age sequence of successive physical states.

But the importance of a study of the components of physical status and physical progress extends even beyond the possibility of reconstructing out of them a quantitative rating of physical condition. A second and in some respects a still greater reason for studying the components of physical status and progress will be plain from the following explanation.

Throughout the period of school life, height, weight, and age are undergoing continuous change; at least it is not normal, even if possible, for height and weight to remain constant during any prolonged interval, say even for six months, not to mention a year or two, and still less 10 years. Now, however, what about physique, developmental rate, nutritional grade, and age schedule or auxodrome?

Each of these, it will be recalled, remains fixed (in health) throughout the entire ten- to twelve-year period of school life in spite of the fact that height, weight, and, more generally, body size are all undergoing continuous change as a result of growth. Thus, the components of physical status and progress may be said to represent the invariants of growth and development. But while these under normal circumstances do not change at all, at least not within the insignificantly narrow limits set by channel width and auxodrome position, they are nevertheless susceptible to great and potentially serious changes. It may therefore be said that the basic purpose of the Grid technique is to enable the physician to recognize when, in what respect, and to what extent a given

child adheres to or departs from a normal pattern of growth and development, the most fundamental and significant feature of which is its invariancy with respect to physique, developmental rate, nutritional grade, and auxodromic advance in spite of continued growth in body size.

Under the favorable conditions of health, growth and development should, therefore, take place (1) without alteration of physique, (2) at an average rate of one level line per month, and (3) on a schedule specific for the child in question. In practice, these conditions simply require that a child keep to his channel and to his own auxodrome. Failure to do so calls for investigation. For that purpose a hint as to whether nutritional, endocrinologic, or other matters are chiefly involved may often come from the specific changes that one or more of the normally invariant components of physical status and progress will disclose.

SUMMARY

This paper is concerned with a detailed account of the components which are employed in the Grid technique to represent and define the physical status of growing children at a given moment and their physical progress from one observation to the next. To evaluate status it is necessary to fix upon three components: physique, development, and nutritional grade. To evaluate progress one needs to note only from a child's channel course and auxodrome how sequential states behave with the passing of time.

Photographs of children arrayed in accordance with their Grid positions help to illustrate what physique, development, and nutritional grade signify when taken singly or in various combinations.

The clearest understanding of what physique signifies is obtained by comparing children in different channels who have reached the same developmental level; conversely, the best illustration of development is given by comparing children in the same channel who have reached different levels. Thus, for children in the same channel, increasing level leads merely to increase in absolute body size and not to alterations in physique.

The role of age, which is concerned only with progress, is fully discussed. The sole value of age, in the matter of judging growth and development, is its function of determining, with the help of a child's auxodrome, whether that child is keeping to his own specific schedule of development or not.

The outstanding and fundamentally important characteristic which physique, developmental rate, nutritional grade, and age schedule (auxodrome) possess is that in health they remain constant during the prolonged ten- to twelve-year period of school life in which children through the impetus of growth are undergoing continuous and ultimately great change in body size. The invariancy of these components when all

else is changing sets the pattern of satisfactory growth no matter how children may differ or be alike in other respects. An evaluation of growth and development for the purposes of assessing the physical condition of children thus depends far more upon noting whether changes have occurred in the components that should normally remain constant than upon dealing with attributes that are changing from day to day.

I wish to acknowledge my indebtedness to the staff of the Children's Fresh Air Camp of Cleveland for their cooperation and help in obtaining the photographs shown in Figs. 1, 2, 3, 5, 6, 7, and 9, and to Lieut. William G. Zantiny, M.C., U. S. Army, for taking the photographs.

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AN ASSOCIATION OF GASTROINTESTINAL ALLERGY WITH THE CELIAC SYNDROME

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THE clinical picture of the celiac syndrome was first described in 1888 by Gee.[1] Since then, although many investigators have studied the etiology of this disorder and the metabolic changes occurring in it have become more clearly defined, there has developed no unanimity of opinion as to the underlying cause. Some of the causes propounded serve to explain certain types of steatorrhea, but none adequately explains the pathogenesis of the celiac syndrome as originally described. The possible etiologic factors as set forth in the monograph by Parsons[2] are numerous and serve only to illustrate the existing confusion:

1. Disturbance of gastrointestinal secretions
   a. Gastric
   b. Biliary
   c. Pancreatic
2. Disturbance of the gastrointestinal tract
   a. Chronic enteritis
   b. Obstruction of lacteals
   c. Functional disturbances (motility)
3. Metabolic disorder
4. Endocrine disorder
5. Vitamin deficiency
   a. Vitamin A
   b. Vitamin B

Although deficiency of hydrochloric acid has been reported in cases of celiac disease, Parsons, in a series of 200 cases, could find no evidence of achylia gastrica. Neale[3] also noted normal gastric juice in a number of patients. When one considers that the plausible way in which gastric secretions might induce the disease is by some effect of such secretions on the juices of the intestine which are associated with fat digestion, one would have to demonstrate an abnormality in the latter. Yet, no such abnormality has been found. Regarding the deficiency of bile, one notes that Cheadle, in 1903,[4] referred to this disease as an acholia. However, duodenal drainage yields normal biliary secretion. Parsons proposed that perhaps there was a deficiency of a bile salt; namely, desoxycholic acid. However, he went on to prove that no deficiency of such acid existed. Others have felt that perhaps the intestinal juice in celiac patients showed an alkalinity which interfered with the secretion and action of bile. Neale has refuted this point by demonstrating that the pH of

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duodenal contents was 6.9 or normal. The last of the intestinal secretions which have come under observation in celiac disease have been those of the pancreas. Although one form of steatorrhea, that associated with cystic fibrosis of the pancreas, has been attributed to a deficiency of these enzymes, especially trypsin, Andersen[5] has found no alteration in pancreatic enzymes in cases of celiac disease. The other point against any deficiency of the intestinal juices is that the fats found in the stools show definite evidences of digestion.

Herter,[6] in 1908, was the first to describe the disease in America. He attributed the disease to infection and called attention to a gram-positive intestinal flora. Other individuals have suggested dysentery organisms as the causative agents. But it has not been possible to demonstrate consistently in the morbid anatomy any signs of infection, any evidence of the obstruction of the lacteals, or any other morphologic alteration which might explain the defect in fat absorption. Yet it is possible that steatorrhea in some cases might be the result of obstruction of the lacteals.[7] Radiographic studies in patients with the celiac syndrome have demonstrated an increased motility in the small intestines and a tendency to clumping of barium which may be caused by alternation of atonicity and spasticity of the intestinal musculature.[8] However, explanations of this finding are unsatisfactory.

Various workers have attributed the celiac syndrome to a disturbance of the metabolism of either fat or glucose. This work has not withstood the test of time, and there is common agreement at present that the difficulty lies in faulty absorption rather than in digestion or in subsequent metabolism of food substances. Although pluriglandular disturbances have been vaguely referred to as causes of celiac disease, it was not until the work of Verzar[9] that any one gland was shown to play an etiologic role in steatorrhea. Verzar showed that fat absorption ceased after adrenalectomy, resulting in the development in young animals of a large abdomen, steatorrhea, osteoporosis, and a hypochromic anemia. Verzar thought that this condition closely simulated the picture of Gee-Herter disease. He explained the phenomenon as due to lack of phosphorylation in the utilization of both glucose and lipids, maintaining that these were absorbed from the intestinal tract as hexose phosphoric acid and phospholipids, respectively. However, if an adrenal disturbance were the underlying cause of celiac disease, one would expect to find other evidences of adrenal insufficiency. Yet such evidences are not encountered. Verzar calls attention to the fact that in adults with sprue, one sees a skin eruption which he considers similar to that of Addison's disease. However, in children with celiac disease such an eruption has not been reported.

Vitamins naturally have come in for their share of attention. It has been noted that in some of the reported cases, there has been an evidence of vitamin A deficiency. However, vitamin A deficiency has not been

offered as a possible cause of the disease but has been attributed to a lack of absorption of this vitamin. Factors in the vitamin B complex, on the other hand, have been strongly suggested as possible etiologic agents. Verzar again showed that the mechanism which produced steatorrhea in adrenalectomized animals was the result of the inability of the animal to transform lactoflavin to flavin phosphoric acid, vitamin B_2, by showing that the administration of flavin phosphoric acid as present in liver extract or yeast caused the steatorrhea in adrenalectomized animals to disappear.

Thus it seemed that the lack of vitamin B_2 might produce a steatorrhea. In cases of tropical sprue and in certain cases of nontropical sprue, this possible etiology has been further substantiated by the associated findings of certain features of vitamin B deficiency such as glossitis and a skin eruption which closely resembles pellagra. Additional support has been offered in other studies, including one by Manson-Bahr,[10] which indicates that liver extract and vitamin B preparations tend to cure certain cases of sprue. However, in celiac disease, as observed in children, the associated signs of vitamin B deficiency are usually lacking, and it is known that liver extract or vitamin B preparations usually fail to relieve the condition.

Thus when the factors proposed as bearing an etiologic relationship to the celiac syndrome are reviewed, it is found that the pathogenesis of this disorder is obscure. In studies of the celiac syndrome carried out over the past two years, it has come to our attention that there may be an association of gastrointestinal allergy with certain cases of celiac disease. Riley,[11] in 1939, described celiac symptomatology associated with eczema and referred to the syndrome as possibly a metabolic eczema. Kunstadter[12] has recently reported gastrointestinal allergy in patients with the celiac syndrome.

Our observations, which tend to confirm the association of allergy with the celiac picture, fall into three categories:

1. We have been able to demonstrate in each patient who presented evidences of celiac disease and who has come under our care during this period some evidence of gastrointestinal allergy as indicated by scratch or intradermal sensitization tests.

2. Among the records of this clinic we have found outspoken cases of gastrointestinal allergy with symptoms that simulate very closely those of celiac disease.

3. In certain other types of allergic conditions we have observed interference with absorption of food substances from the gastrointestinal tract similar to that observed in celiac disease.

Case reports of patients with the celiac syndrome may serve to illustrate the association of the disorder with gastrointestinal allergy.

Case 1 (486346).—G. V., a 3-year-old white female, was first seen in the clinic in July, 1941, with a chief complaint of abdominal distention. The family history was negative. The child had been born at term by normal labor and spontaneous delivery.

Weight at birth was 7 pounds, 5 ounces. She had developed normally for the first two years of life. One year before admission, marked abdominal distention was noted, and she began to have loose stools which were extremely bulky, gray, and foul smelling. In the two to three months before admission, she vomited occasionally immediately after meals; the stools had increased in number to three to five per day and had become bulkier and more foul smelling. On admission she was found to be a well-developed but markedly undernourished white child who appeared to be less than the stated age of 3 years. Her height was 33½ inches, weight was 19 pounds, temperature was 102.6° F. Physical examination was negative except for a mild respiratory infection and evidences of undernutrition and marked abdominal distention. The blood count on admission showed a hemoglobin of 43 per cent; red cell count, 1,600,000; white cell count, 3,500, of which 16 per cent were polymorphonuclear leucocytes, 72 per cent lymphocytes, and 12 per cent monocytes. The urine was normal. Stools were slate gray in color, somewhat soft, and of foul odor. No blood, mucus, or neutral fat was observed. Tuberculin and Kahn tests were negative. Serum calcium was 9.2 mg. per cent; phosphorus, 4.5 mg. per cent. Total lipids were 514 mg. per cent. A glucose tolerance test revealed a fasting level of 60 mg. per cent. One-half hour after the ingestion of glucose the level was 85 mg. per cent; in one hour it was 95 mg. per cent; in two hours, 67 mg. per cent; in three hours, 58 mg. per cent; and in four hours, 73 mg. per cent. The child was placed on a diet which consisted chiefly of protein milk, cottage cheese, bananas, and lean meat. She was also given cevitamic acid, thiamine chloride, and drisdol. On this diet she gained a total of twelve pounds in a period of two months. In December, 1941, two months after discharge, she had again developed episodes of vomiting following the ingestion of food, together with increasing abdominal distention and diarrhea. She appeared again as an undernourished, pale child now measuring 36 inches in height and weighing 25¾ pounds. Marked abdominal distention and a pitting edema of the ankles were the positive physical findings. The edema of the lower extremities was thought to be due to hypoproteinemia, since the plasma protein level was found to be only 2.7 Gm. per cent. The edema disappeared with blood transfusions and a diet of skimmed milk and cottage cheese, to which were slowly added lean meat, banana, and orange juice. In March, 1942, a vitamin A absorption test was performed. It was found that her fasting vitamin A level was 15.9 μg per cent; four hours after the ingestion of the test dose of vitamin A, it had risen to only 18.5 μg per cent. In April, 1942, because of poor response to treatment, intradermal tests for the common foods were performed. The child was found to be strongly reactive to orange, beets, and bananas, and less so to apple. As a result of the intradermal tests, the foods producing positive reactions, including banana and orange juice, were removed from the child's diet. Subsequently a vitamin A absorption test was repeated. At this time it was found that the vitamin A level was 17.2 μg per cent; four hours after the ingestion of the test dose of vitamin A, the blood level had risen to 43.0 μg per cent. The child was seen again in July, 1942, at which time she was still undernourished and had slight abdominal distention. However, she was symptom free and had regained the weight she had lost.

CASE 2 (489472).—S. B., a white female, was seen in October, 1941, at the age of 2½ years with a chief complaint of recurrent diarrhea of two years' duration. The family history was negative except for hay fever in the mother. The child had been born at term by normal labor and spontaneous delivery. The neonatal period was normal, and she continued to do well during the time that she was breast fed. At the age of 5 months she was placed on a formula containing evaporated milk and at the age of 7 months, on powdered milk, on both of which formulas she did poorly. She tolerated cod-liver oil badly, even having emesis after the ingestion of one of the concentrates. Orange juice seemed to produce diarrhea. At the age of 1 year the

child began to have one to two stools daily which were large, foamy, gray, and foul smelling. Mucus was noted on occasion, but at no time was blood observed. During this period the child had frequent upper respiratory infections and failed to gain weight. On admission she was a fairly well-developed, undernourished, chronically ill white child. Her height was 35 inches, and weight was 23½ pounds. The remainder of the physical examination was negative except for a moderately distended abdomen. X-ray examination of the child's chest was negative. Roentgenograms of the gastrointestinal tract showed a delay in passage of the test meal through the small bowel with moderate dilatation of loops of small bowel and distribution of the barium in clumps. The stools repeatedly showed positive reactions for neutral fat. Hemoglobin was 80 per cent; red blood count, 5 million; white cell count, 15,000, of which 49 per cent were polymorphonuclear leucocytes with 1 per cent eosinophiles and 50 per cent lymphocytes. The tuberculin and Kahn tests were negative. The blood cholesterol was 116 mg. per cent. A glucose tolerance test showed a fasting level of 72 mg. per cent; one hour after the ingestion of glucose it was 105 mg. per cent; in two hours it was 145 mg. per cent; in three hours, 133 mg. per cent. Scratch tests with foods and inhalants were made, and at this time all were found to be negative. The child was sent home on a modified celiac regime, her diet consisting of cereals, bananas, skimmed milk, soft-boiled eggs, strained fruits, lean meats, and potatoes. In view of the finding of neutral fat in the stools, she was given pancreatin, 5 gr., with meals. She was seen five months later, at which time her weight was 30 pounds, a gain of eight pounds. Nine months after her first visit, in June, 1942, she was again seen. Her height was 36¾ inches, and weight was 32½ pounds. The physical examination was again negative except for slight distention of the abdomen. In the intervening history it was noted that since her last discharge from the hospital, the child had had no infections and no abdominal pain or vomiting until two weeks preceding this visit, when she had been away from home and broken her diet by eating candy, canned fruits, and fresh peas. In that period the stools again became gray, bulky, and foul in odor. Intradermal tests for the foods were performed, and the child was found to react to string beans and peas. The fasting vitamin A level was found to be 21 μg per cent with carotene 33 μg per cent. A vitamin A absorption test was performed, and it was found that the child had no rise in the blood level after the ingestion of the test dose. A glucose tolerance test on this admission was normal. The child was discharged on a diet as before with the exception that string beans and peas were to be eliminated.

CASE 3 (500948).—K. F., a white female, was seen in March, 1942, at the age of 8 years with the chief complaint of celiac disease. The family history was negative except that the paternal grandmother had asthma and a paternal uncle had hay fever. The child was born after a full-term gestation by instrumental delivery. Weight at birth was 6 pounds, 1 ounce. Her development was normal until the age of 2½ years, at which time she developed episodes of diarrhea which were characterized by loose, large, foamy stools, grayish in color and extremely foul smelling. These episodes had been treated by starvation followed by a diet of scraped apple. However, the child continued to lose weight and at the age of 3 years was first hospitalized. At that time a diagnosis of celiac disease was made, and she was placed on a diet including protein milk and eliminating fats, starch, and sugar. On this regime the child did fairly well and made progress in both growth and development. At the age of 7 years she was again admitted to a hospital where she remained for one month's observation, and the diagnosis of celiac disease was again made. Her diet consisted of skimmed milk, vegetables, fruits, and some meat. On this regime she gained weight and appeared normal except for constant abdominal distention. She had suffered no other illnesses except that on occasion she had had hives. On admission to this hospital the child, 8 years of age, was 47½ inches in height and weighed 46 pounds. The physical examination revealed a child who appeared to be smaller than her stated age but who

presented no abnormal physical findings except for a marked abdominal distention. Stools were large, grayish in color, and foul smelling but contained no neutral fat. The blood showed a hemoglobin of 78 per cent; red cell count, 4,200,000; white cell count, 10,000, of which 55 per cent were polymorphonuclear leucocytes, 4 per cent eosinophiles, and 45 per cent lymphocytes. Urinalyses were negative. Tuberculin and Kahn tests were negative. (Basal metabolic rate was plus four.) Blood chemistry revealed a nonprotein nitrogen of 30 mg. per cent; chlorides, 498 mg. per cent; phosphorus, 3.1 mg. per cent; calcium, 8.6 mg. per cent; total serum proteins, 8.2 Gm. per cent; albumin, 4.3 Gm. per cent; globulin, 3.9 Gm. per cent. Cholesterol was 250 mg. per cent; total lipids, 700 mg. per cent. A glucose tolerance test showed a fasting level of 88 mg. per cent; one-half hour after the ingestion of glucose, it was 116 mg. per cent; in one hour it was 117 mg. per cent; in one and one-half hours, 94 mg. per cent; in two hours, 101 mg. per cent; and in three hours, 94 mg. per cent. A vitamin A absorption test was then made. In a fasting state the blood showed no carotene and a vitamin A level of 25 μg per cent. Four hours after the ingestion of 150,000 units of vitamin A, the level was still 25 μg per cent. Roentgenograms of the gastrointestinal tract showed normal motility but slight distention of the small bowel. The long bones showed delay in ossification but no lines of growth arrest. By skin tests for food sensitivity the child was found to react to bananas, beets, rye, wheat, apple, lamb, oats, tomato, and peanuts. She also showed a strong reaction to house dust. She was discharged on a regime of puréed vegetables, Farina, scraped beef and liver, whole eggs, cottage cheese, and skimmed milk. The bananas and other fruits and vegetables to which the child was sensitive were eliminated from the diet. She was seen two months later, at which time her physical examination revealed no new findings except that the abdominal distention was for the first time markedly decreased and she was having normal stools. Blood studies revealed that her carotene was no longer 0 but measured 166 μg per cent, and her vitamin A level was 32 μg per cent. However, a vitamin A absorption test still revealed an impairment of absorption.

CASE 4 (506318).—B. T., a 13-month-old white male infant, was seen in June, 1942, with the chief complaint of diarrhea which had its origin seven weeks before admission to the hospital. The family history was negative. The patient was born at term by low forceps delivery. His weight at birth was 8 pounds, 11¾ ounces; the neonatal period was uneventful. He was breast fed for a period of ten days and was then placed on Similac. He remained well until the age of 7 months, at which time he was placed on whole cow's milk. Pablum had been added to the diet at the age of 3 months, vegetables and liver soup at 4 months, and eggs at 6 months. At the onset of his illness seven weeks before admission into the hospital, he weighed 22 pounds. The initial symptom was diarrhea, consisting of loose yellowish or greenish stools, containing no blood or mucus. After this condition had persisted for a period of two weeks, he was admitted to a nearby hospital where a diagnosis of celiac disease was made, and the child was placed on a diet which included skimmed milk, bananas, and cottage cheese. During this period of hospitalization the child had two severe episodes of bronchitis, both of which were treated with chemotherapy. On physical examination the patient was found to be a well-developed but emaciated child with a very protuberant distended abdomen. His height was 30 inches; weight 18 pounds, 7 ounces; temperature, 99.4° F. The physical examination except for the protuberant abdomen and marked emaciation was negative. The examination of the blood showed a hemoglobin of 76 per cent; red cell count, 4.9 million; white cell count, 5,700 with 35 per cent polynuclear leucocytes and 65 per cent lymphocytes. The stools were foamy, gray, rather pasty, and foul smelling but contained no neutral fat. Tuberculin and Kahn tests were negative. Agglutination tests against the typhoid, paratyphoid, and dysentery organisms were negative. A glucose tolerance test showed a fasting level of 96 mg. per cent; one-half hour after the ingestion of glucose, the

level rose to 112 mg. per cent; in one hour it was 96 mg. per cent; in two hours, 81 mg. per cent; in three hours, 57 mg. per cent. Vitamin A absorption test showed a fasting state of no carotenoids and a vitamin A level of 3.1 L units. Four hours after the ingestion of 200,000 units of vitamin A, the carotenoids were still zero and the vitamin A was 2.6 L units. Roentgenogram of the chest was negative, while examination of the intestinal tract showed a tendency toward clumping of the barium in its passage through the small bowel. The child was subjected to scratch and intradermal skin tests for the common foods, and positive reactions were obtained against milk, tomato, squash, spinach, grapefruit, and egg white. On a diet omitting these foods, the baby was symptom free and gained eight pounds in two months.

COMMENT

It may be noted that in each of these patients it was possible by skin tests to demonstrate some evidence of food allergy. The results were particularly interesting in two patients, namely, G. V. and K. F., in whom there were strongly positive reactions to bananas, which are often considered an important part of the celiac diet. The elimination of foods to which there were positive reactions although not followed by dramatic response was followed by very definite evidences of improvement. The improvement could be observed in the general condition of the patient and was demonstrable by studies of absorption of glucose and fats from the gastrointestinal tract. Thus in the case of G. V. the absorption of vitamin A showed a definite increase after the elimination from the diet of the foods to which she was sensitive. Initially, there had been an increase in the blood level of only 2 μg of vitamin A during a four-hour period following the ingestion of 100,000 units, whereas after the allergens were removed from the diet, the child showed by a similar test a rise of 36 μg. Although not normal, the absorption of vitamin A seemed markedly improved as compared with her previous state. In the case of K. F., however, there was no marked improvement in the vitamin A absorption within the period of a few days after the withdrawal of food allergens, but there was a return of the carotenoids to normal level. This was considered to be possibly one of the first signs of amelioration of her condition, which might be followed by an improvement of vitamin A absorption. In some of our patients, evidences of allergy as shown by the skin tests, although demonstrable, have not been remarkable. However it is well known that skin testing is not a dependable method for the determination of food allergies, and important food sensitizations may be missed by these tests and yet be discoverable by ingestion studies.

From these studies we assumed that an association might exist in certain patients between the celiac syndrome and gastrointestinal allergy. The problem promptly arose as to whether the food sensitivity might be due to the absorption of unchanged food substances from the intestinal tract as a result of a disturbed absorptive mechanism associated with celiac disease or whether the celiac disease developed because the patient

had in early infancy, by reason of the absorption from the intestine of unchanged proteins, developed sensitizations which manifested themselves in the form of the celiac syndrome. In other words, one could not determine, in the association of gastrointestinal allergy with celiac symptomatology, whether the celiac manifestations were responsible for the development of the allergy or whether food allergy arising in early infancy might be responsible for the subsequent development of celiac disease.

In view of the observation of the presence of food allergies in patients with celiac disease, it seemed worth while to select from records of this hospital patients with outspoken gastrointestinal allergy to see if the symptoms presented by these patients might have any relationship to those of the celiac syndrome. From the records we have selected the following two cases which are interesting because the symptoms manifested were those of celiac disease and in each case at one time the diagnosis of celiac disease had been made, to be dropped subsequently for the diagnosis of gastrointestinal allergy.

CASE 5 (168520).—D. T., a white female, was seen in 1927 in the Pediatric Clinic at the age of 2 years with the chief complaint of marked malnutrition. The family history was essentially negative. The child was born at term by normal labor and spontaneous delivery. The weight at birth was 9 pounds. She was breast fed for two months, then placed on a lactic acid milk formula. She did well for nine months, attaining the weight of 18 pounds. Subsequently she became irritable, her appetite became poor, and while offered a soft diet, cod-liver oil, and orange juice, she became a feeding problem. At the age of 1 year she had pneumonia and was acutely ill for three weeks but following this episode had no further respiratory infection. However, she then developed diarrheal stools which were green and liquid. She became listless, stopped walking and talking, and developed an increasing pallor. The physical examination on admission at the age of 2 years showed an undernourished child markedly emaciated, especially in the extremities where there was an associated atrophy of the muscles; the weight was 17 pounds. Other positive findings were abdominal distention and beading at the costochondral junctions. Roentgenograms of the long bones revealed signs of rickets. During the period of observation the stools were gray in color, bulky, and extremely foul smelling. On the basis of the history and the chemistry of the stool, a diagnosis of celiac disease was made. The child was placed on a high protein, low fat diet derived largely from fat-free lactic acid milk, on which regime she gained five pounds and was discharged from the hospital. Four months later she was doing well on a diet of 1,000 calories, consisting of 90 Gm. of protein, 90 Gm. of carbohydrate, and 30 Gm. of fat. However, the mother at this time stated that the child did not like the cheese or the milk. The weight was 25 pounds, a gain of three pounds since her previous hospitalization. This patient was again seen in March, 1928, almost a year after her initial visit, at which time she was brought to the Clinic with a chief complaint of vomiting and refusal of food. There was a history that the stools were frequent, occurring three to four times a day, that they were yellow and had an extremely foul odor. She showed marked abdominal distention and evidence of weight loss, her weight at the age of 3 years being 21 pounds. She was placed on a diet of protein milk, cottage cheese, and overripe bananas, and liver extract was administered intramuscularly. In May, 1928, sensitization tests were performed, and the child was found to react strongly to cow's milk, whole wheat flour, beets, tomatoes, celery, and figs and to react slightly to egg white,

spinach, carrot, soy beans, cocoa, and string beans. She was then placed on a diet eliminating these foods and including goat's milk, bananas, vegetables, eggs, and orange juice. On this regime the diarrhea stopped and the child improved. In February, 1929, at the age of 4 years, the patient was admitted because of an attack of acute diarrhea of one week's duration. The diarrhea consisted of five or six greenish watery stools daily which occasionally contained both blood and mucus. Her examination was again negative, except for marked abdominal distention. Her height was 33 inches; weight, 26 pounds. Skin tests showed that the child reacted only slightly to cow's milk, so it was replaced in her diet. Gradually the stools stopped being liquid in character and became yellow and well formed. The patient was next seen in 1931, at the age of 6 years, four years after her initial visit. In the interval she had been on a regular diet with some limitation of fats and had done well until one month before admission when the diarrhea, consisting of loose stools containing some mucus, recurred. At this time physical examination revealed a well-developed and well-nourished apparently normal white female. There was no evidence of abdominal distention. The stools showed no excess of fats. Subsequently the child was seen on a number of occasions. Her growth continued to be normal and she remained well, except for repeated episodes of acute gastrointestinal disturbance, about once or twice a year, characterized by vomiting and loose liquid stools.

CASE 6 (380651).—A. W., a white female, was seen in 1936 at the age of 2 years with the chief complaint of intermittent diarrhea of one year's duration. The child's family history was negative except for the story of one cousin who had asthma and of a maternal aunt who had urticaria. The patient was a full-term baby, born after a normal labor by spontaneous delivery. Weight at birth was 7 pounds. She developed normally until the age of 1 year, at which time she began to have intermittent attacks of diarrhea. During the last attack before her visit to the hospital, she averaged ten stools daily. These stools were gray in color and foul smelling. Previously the stools had been greenish yellow. Past history revealed that at the age of 5 months, upon being fed albumin water, the child had developed an attack of diarrhea which was accompanied by hives. It was also noted that every time she was given egg yolk she developed diarrhea. On physical examination she seemed a well-developed, slightly undernourished, little girl who appeared to be about the stated age of 2 years. Height was 33¼ inches; weight, 23 pounds. The remainder of the physical examination was negative except that the abdomen was noticeably distended. Because of the history of sensitivity to foods, the child was skin tested and was found to react strongly to egg white, egg yolk, English walnuts, potatoes, and squash. She was found to react less markedly to barley, rice, corn, navy beans, and mushrooms. The child was placed on a diet eliminating these substances. When seen two years later, she had remained free from gastrointestinal disturbance. Physical examination showed her to be a well-developed and well-nourished girl 4½ years of age.

From these case histories, it seems clear that the symptomatology of gastrointestinal allergy may simulate that of celiac disease. As a further point of interest which might bear on this subject, it seemed desirable to investigate other types of allergy such as atopic eczema and asthma which might be attributed to food sensitivity, but in which there may be no gastrointestinal symptoms, to see if in these disorders interference with gastrointestinal absorption would be encountered. It was decided to measure vitamin A absorption as a chemical determination which could be considered indicative of such gastrointestinal dysfunction. In

the normal child, as shown by May and his associates,[13] the vitamin A level in from three to five hours after the ingestion of 0.1 c.c. of oleum percomorphum per kilogram of body weight rose an average of 129.7 units. In patients with celiac disease these investigators observed an average rise of only 8.2 units, the greatest rise observed being 26.5 units as contrasted with the lowest rise in normal infants and children of 52 units. Though an impairment of vitamin A absorption is not peculiar to celiac disease and has been noted in such conditions as cystic fibrosis of the pancreas, congenital biliary atresia, cirrhosis of the liver, cretinism, and, at times, in pneumonia, it seems significant that in celiac disease it was in almost every case abnormally low. As a check of our determinations, in which vitamin A was recorded in micrograms,* similar tests were made on control cases. A group of three patients, one with malnutrition, one with congenital syphilis, and one with a chronic pneumonitis, showed an average rise of vitamin A in the blood of 172 μg per cent compared with two patients with congenital biliary atresia in whom no rise was observed and as compared with an average rise of 0.8 μg per cent in our patients with celiac disease.

The first of our patients with definite allergy, unassociated with gastrointestinal symptoms, had atopic eczema. A rise of only 17 μg was obtained in four hours after the ingestion of the preparation of vitamin A. The second patient, a 5-year-old white female, who was admitted during an acute asthmatic attack and who was also demonstrated by subsequent skin tests to have marked food sensitivity, had a zero absorption of vitamin A during the episode of acute asthma. However, several days after recovery from the asthmatic attack, the child showed an absorption of vitamin A to permit a rise in the blood level of almost 50 μg. A third patient, a child with asthma and mild food sensitivity, showed a vitamin A absorption sufficient to show a blood level rise of only 19 μg. The average rise was 12 μg in the three patients with proved allergy.† It is interesting to note that in almost all of our patients with celiac disease and in those other patients in whom interference of vitamin A absorption was encountered by the above described tests, there were no abnormally low levels of vitamin A in the initial measurements of the blood. However, in several instances the carotenoids were abnormally low in the initial blood determinations. Thus, despite the impaired absorption fol-

*The method used for these determinations was that of Kimble (J. Lab. & Clin. Med. 24: 1055, 1939). The factors used for the conversion of L units to micrograms per cent were determined by Horton, Murrill, and Curtis (J. Clin. Investigation 22: 387, 1941). The equations used are repeated below for convenience.

Carotene determination:

L_{440} value $\times$ 857.0 = μg per cent carotene

Vitamin A determination:

[L_{328} value for vitamin A $-$ (L_{440} value for carotene $\times$ 0.14)] $\times$ 12.6 = L_{328} units of vitamin A

$$\frac{L_{328}\text{ units}}{5.12} \times 10^2 = \mu g \text{ per cent vitamin A}$$

Using these figures, the normal range of values has been found to be:

Carotene	50 to 360 μg per cent
Vitamin A	20 to 43 μg per cent

†These represent selected cases from a study still in progress of absorption of substances from the gastrointestinal tract in patients with various types of allergy.

lowing ingestion of large doses of vitamin A, none of our patients showed definite evidence of vitamin A deficiency.

SUMMARY

From the observations recorded, it seems that there is, at times, an association of gastrointestinal allergy with the celiac syndrome. Whether the allergy is secondary to a disturbance of absorption dependent on the celiac syndrome or whether the food sensitization precedes and is responsible for the symptomatology of celiac disease is not clear. The added observation that absorption from the gastrointestinal tract of a fat-soluble substance, vitamin A, may be impaired in conditions known to be due to allergy but in which gastrointestinal symptomatology is minimal suggests that degrees of impairment of absorption may occur on an allergic basis and that gastrointestinal allergy may bear a causal relationship to the celiac syndrome.

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American Academy of Pediatrics

Proceedings

TWELFTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

CHICAGO, ILL., NOVEMBER 5-7, 1942

Round Table Discussion on Nutrition and Deficiency Diseases

Chairman: W. H. Sebrell, M. D., Chief, Division of Chemotherapy, U. S. Public Health Service, National Institute of Health, Bethesda, Md.

Secretaries: W. L. Crawford, M.D., Rockford, Ill.
Roger L. J. Kennedy, M.D., Rochester, Minn.

PROF. CONRAD A. ELVEHJEM, MADISON, WIS.—Vitamin B and its various components are classified as water-soluble vitamins because the individual chemical compounds are soluble in water. However, the degree of solubility of the various members of this group varies. Some, such as ribroflavin, have a low degree of water solubility, others dissolve much more readily.

Although these vitamins are grouped together because of their solubility, they differ markedly in chemical structure and function.

Of the various members, thiamine or thiamine chloride is the better known. It is a white crystalline compound with a salty taste and a yeastlike odor. It is rapidly destroyed in neutral or alkaline solutions. In acid solutions it withstands heat for about one-half hour. It is very stable in dry state. It is oxidized only by strong oxidizing agents. The sulfites readily destroy it.

In foods and in tissues it occurs both in the free form and as thiamine pyrophosphate or cocarboxylase.

Pyruvic acid accumulates in the tissues if thiamine is deficient. The symptoms of deficiency, that is, beri-beri, are thought to be due to this accumulation of pyruvic acid.

Wilder and associates described the symptoms of thiamine deficiency in the human being. These consist of depression, irritability, quarrelsomeness, and fearfulness.

Some degree of anemia has also been described, but there is some question as to the nature of the relationship of this to vitamin B deficiency.

Methods of Determination.—Although the official method for the estimation of thiamin is the rat assay procedure described in the U.S.P. XI, 1939 Supplement, the thiochrome and the yeast fermentation methods are suitable for most foods.

Distribution of Thiamine.—Among the foods best supplied with this vitamin are peas, beans, oatmeal, whole wheat, lean pork, and peanuts.

In the average American diet thiamine is supplied to the body as follows: 25 per cent from milk, 25 per cent from meat, 25 per cent from vegetables, and 25 per cent from all other foods.

There is fair agreement in regard to the daily requirement of thiamine. According to the Food and Nutrition Board of the National Research Council, the adult daily requirement is 1.5 to 2.3 mg. The U. S. Food and Drug Administration suggests that 1 mg. is adequate for the adult who takes 3,000 calories of food daily.

The daily requirement increases in individuals with increased nutritional demands. High fat diets spare the demand for thiamine.

There is a factor in some foods, particularly fish, which destroys B_1 rapidly. Observations which have been made on fox and mink farms have shown that feeding of fish (for example, carp) results in a condition of vitamin B_1 deficiency. The importance of this observation in diets of human beings has not been determined. The substance which exerts the deleterious effect is thought to be in the nature of an enzyme.

CHAIRMAN SEBRELL.—The observations which have been made on the effect of the fish diet suggest the possible existence of an anti-B_1 vitamin.

PROF. ELVEHJEM.—

Riboflavin.—Riboflavin is an orange-yellow, crystalline compound which emits a yellow-green fluorescence in aqueous solution. It is heat stable but very labile when exposed to sunlight or to ultraviolet light.

It occurs in nature in both the free and combined states.

It functions in the body as a component of several enzyme systems. These are reduced in riboflavin deficiency.

Evidence of deficiency in the rat are dermatitis and changes in the eyes, including cataract. In chicks a paralysis develops which is related to the involvement of the sciatic nerve. In the dog myeline degeneration of peripheral nerves has been reported. When rats are on an ordinary diet, the signs of riboflavin deficiency are not as extreme as when the animals are maintained on a high fat diet.

The symptoms of riboflavin deficiency in the human being include inflammation of the lips, fissures at the corners of the mouth, glossitis, dermatitis, and vascularizing keratitis.

Methods of Determination of the Riboflavin Content of Foods.—The older method of assay is the measurement of rat growth. This method yielded results expressed in Bourquin-Sherman units.

The microbiologic method depends upon the measurement of the rate of growth and multiplication of *Lactobacillus casei* in media with various concentrations of riboflavin.

The chemical method which depends upon the degree of fluorescence is also used.

Distribution of Riboflavin in Nature.—Riboflavin is most abundant in liver, milk, and green vegetables. Seeds, which are a good source of thiamin, are a poor source of riboflavin.

Daily Requirement.—According to the Food and Nutrition Board, the daily requirement of riboflavin for an adult is 2.2 to 2.3 mg. per twenty-four hours. The Food and Drug Administration advises a minimum daily intake of 2 mg. One quart of milk will supply such amounts, whereas an ounce of cheese or two eggs will supply one-fourth to one-third of the daily requirement.

There is a pronounced beneficial effect of riboflavin on food utilization.

CHAIRMAN SEBRELL.—Riboflavin deficiency is one of the most widespread of human deficiencies in the United States, as has been shown by Spies in his studies in Birmingham, Ala. This is also indicated by dietary survey data.

DR. J. D. BOYD, IOWA CITY.—Are there differences in the riboflavin requirements of different individuals?

CHAIRMAN SEBRELL.—Yes, there appear to be such differences, but the explanation is not at hand.

DR. BOYD.—Do you feel that 4 mg. per day will care for the requirement of everyone?

CHAIRMAN SEBRELL.—Four milligrams per day is a little high. The Food and Nutrition Board suggests a maximal daily intake of 2.7 mg. Experimental work with women showed that a daily intake of 3 mg. was ample.

DR. W. A. NYIRI, NEWARK, N. J.—Is there any effect of irradiation upon the riboflavin content of milk?

PROF. ELVEHJEM.—None.

DR. F. F. TISDALL, TORONTO.—Doctor Drake has shown that if a bottle of milk is permitted to stand in sunlight outdoors for four hours, the riboflavin content falls to zero. However, little or no effect upon the riboflavin content follows such practices as allowing a bottle of milk to stand upon a table indoors.

PROF. ELVEHJEM.—Nicotinic acid or niacin and nicotinamide or niacinamide are white crystalline compounds, which are relatively simple in structure and are heat stable. Their actions are quite similar. However, high doses of the acid are more likely to cause flushing of the skin than are similar doses of the amide.

In the body nicotinic acid functions as a component of two important coenzymes, coenzyme I and coenzyme II. They are important in glycolysis and affect the processes of respiration as well as those of the total metabolism.

Satisfactory demonstrations of deficiency of the coenzymes have not been made on blood, but it is possible to demonstrate a deficiency of the enzymes in muscle. The dog, pig, and monkey are the most satisfactory animals to study and demonstrate evidence of nicotinic acid deficiency. Just last month the chicken was added to this list.

Symptoms of Nicotinic Acid Deficiency.—There are the symptoms of pellagra in the human being and of the black tongue in the dog and are too well known to require repetition here.

The incidence of pellagra in infants and children has been shown to be as high as the incidence in adults in areas of the country where pellagra is prevalent. The frequency and severity of pellagra in bottle-fed infants are not nearly so great as might be expected from the fact that milk contains such relatively small amounts of nicotinic acid. The explanation for this seems to lie in the fact that the infant who is on a milk diet is able to produce the substance in its body, possibly in the intestine.

Methods for Determination of the Nicotinic Acid Content of Foods.—The older method for nicotinic acid assay of foods involved the use of dogs in which black tongue had been produced. The newer microbiologic method, which depends upon the rate of growth of bacteria, is superior and preferable.

Sources of nicotinic acid are liver, yeast, lean meat, peanuts, potatoes and other vegetables.

The daily requirements for nicotinic acid have been difficult to determine. The Food and Nutrition Board advocates a daily intake for an adult of 15 to 20 mg., with a minimal daily intake of 10 mg. In some pellagra regions the chief article of diet is corn meal. Because of the low nicotinic acid content of corn meal, inhabitants of such areas would have to eat 1,000 Gm. of corn meal daily to secure the minimal protective amount of nicotinic acid. Wheat contains from five to seven times as much nicotinic acid as does corn meal, but 90 per cent of the nicotinic acid is lost in the milling process employed to make patent flour. Oats are low in nicotinic acid. They contain about 1.0 mg per 100 Gm. Liver, kidney, and lean meat are good sources of this vitamin, and a 4-ounce serving will furnish an adequate intake.

Nicotinic acid is quite resistant to heat and therefore not a great deal of it is lost during the process of cooking. For example, in cooking meat there is a loss of about 20 per cent, but this can be recovered in the drippings.

CHAIRMAN SEBRELL.—The loss of vitamins during cooking is a very important matter. Unless the approximate degree of loss is known, one may be misled into thinking that foods rich in vitamins in the uncooked state will yield adequate vitamin intakes to the users after such foods have been cooked.

Pellagra is primarily a disease of children. Those in the age group of 2 to 15 years (approximately) appear to be most frequently affected. In the great majority of instances the disease is relatively mild, and, at least in the past, most of these children were untreated.

In some cases of pellagra there is redness of the pharyngeal and buccal mucous membranes and ulcerative stomatitis. Smears may reveal the presence of Vincent's organisms. Response of these lesions to the administration of nicotinic acid has led to the belief on the part of some that nicotinic acid is more or less specific for infection with Vincent's organisms. It is more likely that the presence of the organisms is favored by the lesions of pellagra and that healing takes place when the deficiency has been corrected. Evidence that supports the view that the organisms appear secondarily is afforded by their presence also in the mouth in other conditions.

DR. MURPHY.—Does the requirement of nicotinic acid differ from that of nicotinamide?

CHAIRMAN SEBRELL.—No. The dose of each is the same. However, the use of nicotinamide is preferred. It causes fewer reactions of flushing or burning sensation in the skin. Nicotinic acid causes the same degree of reactions whether it is administered in usual or in very large doses. Other symptoms are rare and mild. Occasionally there is some cramplike abdominal pain following its ingestion.

PROF. ELVEHJEM.—The history concerning pyroxidine (vitamin B_6) is a long one. It was first referred to as the rat acrodynia or as the rat dermatitis factor. In 1939 it was isolated in pure crystalline form. It is a white, crystalline, slightly bitter-tasting compound. Chemically it bears a rather close relationship to nicotinic acid, differing in respect to some of the side chains.

The function of pyroxidine in the body is unknown. It may be related to some enzyme system or systems. It may have something to do with unsaturated fatty acids possibly in the synthesis of fats from protein.

It is required by the chick, the dog, and the pig. In dogs a deficiency of pyroxidine causes a microcytic hypochromic anemia.

In pigs, a deficiency results in epileptic-like fits.

Symptoms of Pyroxidine Deficiency in Human Beings.—There are no clear-cut symptoms of pyroxidine deficiency in human beings. It apparently supplements nicotinic acid in promoting healing of the lesions of pellagra. Cheilitis heals more promptly if it is administered.

Requirement of Pyroxidine.—It has been difficult to determine the daily requirement of pyroxidine. Some, in fact, have questioned the necessity of this compound for proper body metabolism. By calculation, mostly from animal experimentation, the amount necessary has been set at 2 mg. per twenty-four hours.

Determination of Pyroxidine in Foods.—There is no reliable assay method available except the rat growth method.

Distribution of Pyroxidine in Foods.—Pyroxidine is present in liver, yeast, cereals, legumes, and milk. Whole wheat contains about 0.5 mg. in each 100 c.c.; meat contains about the same amount, and milk contains about 2 mg. per quart. It does not occur very widespread in foods. It is quite stable. There is a loss of about 50 per cent of pyroxidine, or B_6, in milling white flour, as compared with a loss of 90 per cent of niacin.

CHAIRMAN SEBRELL.—Pyroxidine, or vitamin B_6, has been used in the treatment of several conditions. It has been used in the treatment of patients

suffering from parkinsonism. Some improvement has been reported in a few of these patients. There have been some suggestions also that lack of pyroxidine bears some relation to muscular weakness. I have been unable to evaluate the reports in the literature dealing with the effects of vitamin B_6 on the condition of patients with progressive muscular dystrophy.

PROF. ELVEHJEM.—The composition, structure, and place of the rest of the members of the B complex in the metabolism of human beings are not well known.

Pantothenic Acid.—This substance was formerly referred to as the "filtrate factor." Although the so-called filtrate fractions prepared from liver were effective in the prevention of black tongue in dogs, pellagra in human beings, and dermatitis in chicks, it was demonstrated as soon as nicotinic acid was shown to be the anti-pellagra factor that the activity of these fractions in the prevention of chick dermatitis was due to a separate and distinct factor. Shortly thereafter the chick factor was shown to be pantothenic acid, which was known to be a growth factor for yeast and bacteria. It is known to be a peptide with certain peculiarities of structure. It is manufactured in the form of a salt. It is not hydrolyzable in neutral solution but can be hydrolyzed in alkaline solutions.

The function of pantothenic acid is not known. It apparently is related to pyruvic acid metabolism. Rats grow poorly on a pantothenic acid-deficient diet. When deprived of this substance, their hair becomes gray in from two to three weeks. Acute deficiency in dogs results in low values for glucose, chlorides, and protein in the blood. In chicks a deficiency causes changes in the spinal cord similar to those produced by Wintrobe in the spinal cords of pigs. Little is known about deficiency of pantothenic acid in human beings.

Distribution of Pantothenic Acid.—Liver is one of the best sources of pantothenic acid. It contains about 4 to 5 mg. per cent. Meat, fish, and milk are also quite good sources. Cooking results in relatively small loss of the substance. It is used as a calcium salt (occasionally sodium). It is not hydrolyzed by enzymes in the intestinal tract. Five milligrams daily may be the approximate requirement of human beings.

Method of Assay for Pantothenic Acid.—The microbiologic method which depends upon the growth of bacteria is the method of choice for pantothenic acid assay. Fifty per cent of the pantothenic acid content of wheat is lost in the milling process.

Choline.—Choline, which is a component of the phospholipid lecithin, is a well-known substance. It is a colorless, viscous liquid. Choline chloride is a white, crystalline, salty, bitter-tasting substance. It may or may not be a true vitamin.

Choline stimulates growth in rats. Most animals are susceptible to choline deficiency, especially the young. Rats show evidence of deficiency within a few weeks, but there is some evidence that indicates that they may be able to synthesize it to some degree.

Function of Choline.—Choline aids in the formation of phospholipids in the tissues. It allows the formation of acetylcholine. It helps to supply the labile methyl groups.

An adequate amount of choline prevents "slipped tendon" disease in chicks.

Determination of the Amount of Choline.—Choline determinations are based on the formation of an insoluble compound with Reinecke's salt.

Distribution of Choline.—Choline is found in fats containing lecithin. It occurs in meat, cereals, vegetables, and eggs. White flour and polished rice are good sources. The choline content of yeast is variable.

Clinical Use.—Choline has been used as a therapeutic agent in cirrhosis of the liver.

Biotin.—Biotin was first isolated in 1936. It was known as the growth factor for yeast. Its history as a vitamin is bound up with the fact that egg white contains a toxic factor which causes dermatitis and which can be prevented by feeding liver

residue, kidney residue, yeast residue, and egg yolk. It has been determined, therefore, that biotin is identical with the anti-egg white factor. In rats biotin deficiency is produced by feeding an egg white diet.

It has been observed that there may be more biotin in the feces than in the diet. This suggested the idea that bacteria elaborate biotin in the intestinal tract. Some of the sulfa compounds are known to inhibit bacterial growth, and the feeding of succinyl sulfathiazole to rats produces a biotin deficiency.

Symptoms of Biotin Deficiency.—The symptoms of biotin deficiency in the chick are similar to those observed in pantothenic acid deficiency, but these symptoms do not clear up when pantothenic acid is administered.

Requirements of Biotin.—The requirement of biotin has not been accurately determined but has been calculated in a very rough manner as 10 μg. daily as a minimal intake and 100 μg. daily as a maximal intake.

Distribution of Biotin.—Biotin occurs in liver, kidney, yeast, egg yolk, and cereals. There is a loss of about 90 per cent which takes place in the process of milling of cereals. Biotin resists boiling with acid and alkali.

Inosotol.—This is a crystalline, sweet substance which is isomeric with glucose. It is a stable compound. It is found in plants where it occurs as phytin. Denudation of mice responds to inosotol. Deficiency of inosotol does not occur in the rat because of the ability of intestinal bacteria to produce the substance in that animal.

Assay of Inosotol.—The test for the inosotol content of foods depends upon the effect of various concentrations of this substance upon the growth of yeast.

Para-amino Benzoic Acid.—There is no proof that this substance is a vitamin in the diet of animals. It may, however, have some indirect vitamin-like effect. That it is the antigray hair factor is questionable.

Other Factors of the B Complex.—The number of other factors that may be present in the B complex is unknown. Evidence that others exist depends upon the experimental animals used for the study. Thus, the eight already enumerated appear to satisfy all the requirements for B factors in the rat and dog. However, in the chick these eight must be supplemented by 3 per cent liver extract in order to supply what, at present, appear to be three additional factors. The situation in regard to monkeys is somewhat the same. In the guinea pig, at least three other factors are needed. If the eight factors are given to rats that are receiving some of the sulfa drugs, the growth of the animals is retarded. There are, therefore, eight of the B vitamins for which we can write the formula; there may be six to eight additional factors.

DR. J. A. JOHNSTON, DETROIT.—In the attempt to correct deficiencies, is treatment with the B complex preferable to treatment with specific vitamins?

PROF. ELVEHJEM.—In human beings, yes.

DR. JOHNSTON.—Does the feeding of an isolated factor tend to exaggerate the symptoms of deficiency of other factors which may not be present in adequate amounts?

PROF. ELVEHJEM.—No, not in animals.

DR. P. F. BARBOUR, LOUISVILLE.—Is there any difference in the absorption of the natural or synthetic vitamin?

Is the absorption of the different vitamins interfered with by diarrheal diseases such as typhoid fever?

PROF. ELVEHJEM.—The question comes up as to the optimal interval to be observed between doses of vitamins. In dogs we varied the interval between doses by one, two, three, and up to seven days. In the case of nicotinic acid, intervals of a week were found to be less efficient than intervals of one or two days. It

appeared that the animals could hold an adequate supply for periods up to three or four days but not for periods as long as seven days.

DR. BARBOUR.—Does the difference depend upon the absorption or on the synthesis of the natural vitamin?

PROF. ELVEHJEM.—No, the problem is that of holding the vitamin in the system.

CHAIRMAN SEBRELL.—In further answer to Doctor Barbour, there is no difference between the natural and synthetic vitamin products when given in the same dosage. The clinical difference in treatment depends upon the condition of the patient, because you rarely see a single deficiency. Furthermore, in the treatment of deficiency diseases in human beings one of the important things is to give a good diet in addition to vitamin preparations.

In reply to his question regarding diarrhea, any diarrhea creates an increased need for vitamins. In infants with diarrhea the vitamin intake should be much higher than normal.

DR. W. R. SISSON, BOSTON.—If one thinks of celiac disease as a deficiency disease, then large amounts of B are necessary.

Do rats have any gustatory sense for vitamin B?

PROF. ELVEHJEM.—Yes, the work done at Hopkins' appears to show this.

DR. SISSON.—Does homo sapiens also have this gustatory sense?

PROF. ELVEHJEM.—Yes, I believe they would if placed under proper conditions.

CHAIRMAN SEBRELL.—Doctor Elvehjem mentioned the restraint of growth produced by sulfaguanidine and by sulfasuxidine. In some experiments which we performed it was found that they also produce a deficiency of biotin in rats similar to that produced by egg white. This deficiency could be controlled by the administration of biotin even while these sulfa drugs were continued.

Furthermore, in some of the experimental animals an agranulocytosis developed after the biotin deficiency had been corrected. It was found that this could be corrected by the administration of liver extract and that this was effective even though administration of the drug was continued. It is suggested by this study that crude liver extract should be given to human beings who develop agranulocytosis during treatment with the sulfa drugs.

DR. JOHNSTON.—Is there any foundation for the use of biotin in the treatment of thickened flexural eczema?

CHAIRMAN SEBRELL.—Gyorgy called biotin the skin vitamin, and although there is no proved relationship between eczema and biotin deficiency, it is quite possible that biotin may prove to be beneficial in some eczema-like skin lesions.

DR. BOYD.—Is there any relation between B deficiency and acrodynia?

DR. TISDALL.—There is no effect on the symptoms. We used it in two cases. The patients promptly recovered and we thought we had something. In the next five or six patients no benefit was noted.

DR. JOHNSTON.—We have studied the effect of B on the blood pressure of patients with acrodynia and found that it brought the pressure down to normal within twenty-four hours. This occurred quite consistently.

DR. TISDALL.—Large doses of nicotinic acid may appear to improve these patients, though the result of the nicotinic acid is probably merely a drying up of the skin.

DR. C. G. WEIGAND, INDIANAPOLIS.—There is a report in the *Lancet* in which it is stated that infantile eczema responded to treatment with the B complex.

DR. BOYD.—Do you think that Vincent's infection will respond to treatment with nicotinic acid?

CHAIRMAN SEBRELL.—If it is due to nicotinic acid deficiency, yes.

DR. BOYD.—The British report success in the treatment of trench mouth with nicotinic acid.

DR. TISDALL.—

Eye Findings in Riboflavin Deficiency.—It was noted that in rats suffering from riboflavin deficiency there is an invasion of the cornea by blood vessels.

Later this phenomenon was observed in human beings.

The condition was studied by means of the slit lamp (Sydenstricker and co-workers in 1939). Tisdall found this to be difficult in the hands of other than well-trained workers. In order to obtain an accurate and permanent record, a photographic technique was developed. Tisdall exhibited pictures and lantern slides which were made by this special photographic technique. High speed (1/30,000 second) with two-million-watt illumination are used. Magnification × 65 will permit visualization of corpuscles or clumps of corpuscles in the vessels. By this method he was able to show, first, the appearance of the cornea in normal rats and in normal human beings and, second, the progress of the growth of blood vessels into the cornea in animals and patients suffering from riboflavin deficiency and the regression of the newly formed vessels after the institution of riboflavin therapy.

He pointed out that photographs have several advantages over the use of the slit lamp in the study of the corneal changes in riboflavin deficiency. In the first place, the procedure is one which requires very little time. He stated that, with the apparatus set up for use, pictures of the cornea could be made at the rate of about one per minute, including the time required for change of patient before the camera. In addition, the pictures serve as a permanent record. They can be studied at leisure and in series can be used for comparison one with another. Lastly, and of great importance according to Tisdall, they can be used to demonstrate to the individual suffering from riboflavin deficiency the objective appearance of his condition. By such a demonstration the patient's cooperation in his own treatment is much more readily and dependably obtained.

Tisdall listed the symptoms of riboflavin deficiency as follows: headache, sensation of sand under the eyelids, reading intolerance, watering of eyes, tiredness and aching of eyes, dizziness, and decreased visual acuity.

DR. BOYD.—Does the tissue content of riboflavin change before the symptoms begin to disappear?

DR. TISDALL.—The symptoms start to clear up in from ten to fourteen days after the start of treatment. Some chronic cases respond anatomically very slowly as compared to acute cases.

Regarding the riboflavin requirements of human beings, no one can give us more reliable information than can Doctor Sebrell. The requirement varies according to many conditions, such as the presence of infection, the amount of light, the amount of use of the eyes, and whether one is at sea, on land, or up in the air. Snow blindness is due to riboflavin deficiency. We studied 400 Indians living at

the northern end of Hudson's Bay. They do not drink milk. Five per cent of them were blind due to riboflavin deficiency. One woman who had been blind for a year was knitting after she had received treatment for one month. The light there is very strong. Fifteen minutes after sunrise it is stronger there than it is here at noon. The light reflected from the snow is twice as strong as that from the sky.

CHAIRMAN SEBRELL.—The growth of capillaries into the cornea might be interpreted as an effort on the part of the body to supply additional riboflavin to the cornea. We have seen patients with corneal opacities, cascades of blood vessels, photophobia, and lacrimation restored to nearly normal vision after riboflavin therapy. The severe cases resemble cases of acute conjunctivitis. Slit-lamp examination is necessary for differential diagnosis.

DR. TISDALL.—The photograph shows more than can be seen with the slit lamp.

CHAIRMAN SEBRELL.—A few children were studied with the slit lamp, but it was a difficult procedure as it requires the cooperation of the patient.

DR. SISSON.—Is there any age predilection?

CHAIRMAN SEBRELL.—No data are available on that point. It is seen in all ages.

DR. TISDALL.—The environment and diet may mask the picture. A change of environment may cause a latent condition to become manifest.

The conditions which we found among the Indians indicate that they tolerate what we would not tolerate. The widespread and marked visual difficulties would prompt us to seek relief long before the Indian manifests concern.

DR. BOYD.—Does vitamin A deficiency simulate riboflavin deficiency?

DR. TISDALL.—We saw many cases of acute A deficiency that suggested it, but these did not exhibit vascularization of the cornea.

CHAIRMAN SEBRELL.—In closing the session I would like to make a few remarks regarding the National Nutrition Program.

Approximately twenty federal agencies are concerned with nutritional programs, and the Nutrition Division of the Office of Defense, Health, and Welfare has been attempting to coordinate the activities of these agencies.

State Nutrition Committees are now active in every state, and local nutrition committees have been set up in most localities. These committees, in cooperation with the Office of Civilian Defense, will soon conduct a large share-the-meat program as a prelude to meat rationing.

Meat rationing is due to go into effect sometime after the first of the year. This probably will allow two and one-half pounds per person per week of beef, pork, veal, lamb, and mutton. Such meats as poultry, sea food, and organ meats will not be included; therefore, there should not be any shortage of animal protein.

There is also a Nutrition in Industry Program in operation. In many of the industrial defense areas local conditions militate against the proper selection and preparation of foods. One of the objectives of the program is to assure that the midshift meal will supply one-third of the recommended daily nutritional allowance. It is hoped that this objective will be attained by voluntary action. The unions and manufacturers have expressed themselves as being in favor of the plan.

Some of the difficulties to be overcome are to be found in the poor housing conditions, in the wide use of the lunchbox, and in the poor breakfast. Efforts to

improve the nutritional situation are bound up with efforts to improve living conditions and involves a unified community effort.

Progress has been made in the matter of enriching white bread and flour. Probably at least 65 per cent of the family flour is now enriched. The enrichment is still almost entirely on a voluntary basis, although in Louisiana and South Carolina enrichment has been made mandatory by statute. Minimum additions required per pound of flour are: thiamine, 1.8 mg.; niacin, 6 mg.; and iron, 6 mg. In April it is planned to add riboflavin if adequate sources can be developed.

DR. BOYD.—Are the flour pastes such as macaroni enriched?

CHAIRMAN SEBRELL.—No, because of the loss in cooking to which these pastes are subjected.

DR. W. H. THOMPSON, MINNEAPOLIS.—Is there an etiologic relationship between pyridoxine and chorea?

CHAIRMAN SEBRELL.—I do not know of any evidence proving such a relationship.

DR. G. H. GARRISON, OKLAHOMA CITY.—Does vitamin B shortage affect bones and teeth as well as skin, nerves, and vessels?

PROF. ELVEHJEM.—Porosis develops in the chick although ash content is not changed; tendon slippage occurs; perhaps teeth changes occur.

DR. J. H. WALL, WASHINGTON.—Can changes in vascularity be seen by anything other than slit lamp or camera?

DR. TISDALL.—No; except in the early stages it looks like ordinary conjunctivitis.

DR. W. P. LUCAS, SAN FRANCISCO.—Without recourse to the slit lamp or camera, what practical lesson can we draw in giving advice to industry or others?

DR. TISDALL.—The requirements of riboflavin should be increased in workers using their eyes a great deal and in those who work in snow, in sun, on water, etc. Infection also increases the need. Overdosage is inconsequential except for niacin which may cause burning of the skin unless the amide is used.

News and Notes

Notice is hereby given that on and after July 1, 1943, candidates will no longer be accepted in Group I. This applies to physicians who have specialized in pediatrics for ten years or more. After that date all applicants will be placed in the same category.

The Tenth Annual Sale of Easter Seals for Crippled Children, sponsored by the National Society for Crippled Children and affiliated organizations, will be conducted this year from March 26 to April 25. The proceeds from this nationwide sale will be used in a continuous program to advance the welfare of crippled children and adults. The sale of Easter seals offers an opportunity for all citizens to share in this important work of building crippled children into happy and useful men and women.

The National Society for Crippled Children has also published recently a pamphlet entitled *Opportunity*. It is a short story of the development of a program for crippled children during the last two decades. Complete information is given about the Society, its publications and activities. Reference is made to various publications, including *The Crippled Child* and a bulletin on current literature of interest to crippled children workers.

The next meeting of the American Pediatric Society, usually held in the spring, has been postponed indefinitely because of wartime conditions.

Dr. Guillermo Sanchez F. of Guatemala, Guatemala, C. A., has been elected a member of Region V of the American Academy of Pediatrics.

Book Reviews

Infant and Child in the Culture of Today. Arnold Gesell, M.D., Frances L. Ilg, M.D., in collaboration with Janet Learned, M.A., and Louise B. Ames, Ph.D., New York and London, 1943, Harper & Brothers, 388 pages. Price, $4.00.

The publishing of this work is exciting news to anyone familiar with the activities of the Yale Clinic of Child Development. It should be equally exciting to anyone interested in human progress.

For many years Dr. Gesell and his associates have devoted themselves tirelessly to studies in human behavior from the developmental viewpoint. It is to his lasting credit that many years ago he saw the tremendous value of scientific research on growth in its true relation to such modern subjects as pediatrics, education, psychology, psychiatry, and even to the democratic way of life.

During all these years of study and assiduous research, he and his collaborators have published many articles and books which have fascinated and stimulated those who caught the spark engendered in his concept of the meaning of growth. Yet, in all this work, the reviewer has felt a certain reserve, as though the authors hesitated to go on and state the full implications of what they had learned. One turned each last page with an unanswered question: "Does this mean as much as it implies? Is growth and development really the basic science upon which we must depend in building a better world?"

But now, in this complete and beautifully published volume, we can turn down the back cover with satisfaction and resolve with Dr. Gesell and his companions that if we do not get busy and apply what we know to practical care of growing children, heaven help the human race.

The book is written in three parts. The first, Growth and Culture, expands his ideas of the interplay between early growth heredity and the environmental culture. The second, The Growing Child, gives a progressive picture of changing behavior during various stages from intrauterine life to the school age. The third, The Guidance of Growth, makes his important philosophic deductions drawn from the development of vital functions such as eating, sleeping, and elimination in their relation to self-discipline and democratic living. These parts are supplemented by an instructive appendix of factual material which will assist the student who needs this help.

The text is long but packed with facts; it is somewhat prolix, but always pertinent; it is profound, but brilliant and clear in its decisions. Best of all, it is down to earth and practical.

To the pediatrician who wants to understand the meaning of his life's work, to the nurse who does not understand how children "get that way," to the teacher, professor, or college president who tries to deal with problems of human understanding, and even to the practical businessman facing the perplexing changes of modern ways of thinking, this is a "must book." Many important answers will be found here by any thoughtful person willing to delve beneath the surface of behavior.

ALDRICH.

A Height and Weight Survey of Toronto Elementary School Children, 1939. Published by authority of the Hon. James A. MacKinnon, M.P., Minister of Trade and Commerce, Ottawa, 1942, 36 pages. Price, 25 cents.

This report sets forth the statistical results of a survey of children in elementary schools of the City of Toronto taken in November, 1939. The Dominion Bureau of Statistics received the schedules and undertook the tabulation, compilation, and statistical interpretation of the results. Their medical interpretation is the work of Drs. Tisdall and Ebbs and their associates.

An original survey of heights and weights of about 59,000 boys and girls in 1923 is used as a basis of comparison with the present study of 78,000 children. The study was made to show the difference in stature and weight between different economic and personal factors of the occupational class or status of the parents: relief status of the family, the district in which the school was located, the grade in school, the relation to communicable disease and to physical and mental defects, public and private schools, the birthplace of the parents and age differences.

The following conclusions have been drawn from the study:

As indicated previously, the study divides itself into three parts through requirements of tabulation: (1) simple averages of height and weight for all pupils, the only separation being sex; (2) the effect of the various factors of the punch card taken singly; (3) the cross-classifications of the factors of the card in their effect on height and weight. This third part has been carried only to the classification of birthplace against the economic factors and awaits the opportunity to make further tabulations, suggestions upon the form of which will be welcomed.

The results of this study agree with results obtained in similar analyses of heights and weights of school children. The tendency found in British and American surveys toward an increase in average height and weight of from 2 to 5 per cent in a generation is also demonstrated here.

It will be desirable to tie in the results of this survey with work done on nutrition; it is of importance to establish fairly precisely the range within which good or poor nutrition can affect heights and weights. This matter, always vital, is of especial importance in wartime, with the need, even in Canada, to make the most of our food resources, and to maintain a healthy population. Its long-term importance is stressed by the surprising correlation between backwardness at school and poor stature.

It is not suggested here that stature is the sole measure of bodily well-being. In individual cases serious malnutrition may accompany normal height and weight, as was found in some of the defects (Table 14), but for broadly selected groups the present study confirms results obtained many times previously of the effect of environment on height and weight. This is revealed in the individual occupations, district in which the school is situated, relief status, etc.

At the same time, the complete disentangling of hereditary and environmental factors cannot be claimed for this survey. It contains nothing which disproves the possibility that children of relatively prosperous parents are taller because their parents, on the average, are taller (if, for example, tallness is a factor in economic success) as well as through superior environment. Such a separation of factors would ideally require a study of heights and weights of parents in relation to their children. However, the separation of heredity from environment was partially made in the present data by a sorting of each of the economic factors by birthplace; the economic differentials seemed to run through each birthplace. Another unresolved difficulty is the possibility that the effect of nutrition is, in part, a speeding up of growth that would have taken place later in any case, though the uniformity of the differentials with age is an argument against this.

McCULLOCH.

Standards of Child Health, Education, and Social Welfare. Department of Labor, Children's Bureau, Publication No. 287, 1942, 21 pages. Superintendent of Documents, U. S. Government Printing Office, Washington, D. C. Price, 10 cents (in coin or postal money order only).

The summary of standards of child health, education, and social welfare presented in this pamphlet is based chiefly on the general report adopted at the 1940 Conference on Children in a Democracy. From the conclusions of discussion groups covering a broad range of subjects, these standards have been compiled by members of the Children's Bureau staff. The following general subjects have been covered: safeguards of family life, health and medical care for children, educational services in the community, child labor and youth employment, social services for children, economic aid to families, and public administration and financing.

The publication should be of special importance as a guide to states and localities and to agencies under private auspices in the development of the services required for meeting special wartime needs of children.

McCULLOCH.

Preliminary Report on Children's Reactions to the War, Including a Critical Survey of the Literature. J. Louise Despert, M.D., Josiah Macy, Jr., Foundation, New York, 1942, 102 pages. Privately published. Price not stated.

During the course of studies of personality development in normal young children carried out at the Payne Whitney Nursery School under the auspices of the Cornell University Medical School, it became timely to study specific reactions to war stimulus in children who already had been subjects of investigation. A group of seventy-one children who had been at the school from 1932 to 1937 and sixty children who had been under intensive study of anxiety and fears in normal young children by the author from 1937 to 1942 were selected. Of these, fourteen from the first group and forty-three from the second were included as suitable for study.

There is an extensive compilation of the literature on the subject, especially a recent statement by the Union of Soviet Socialist Republics. The general findings in the children studied are given. Two significant observations were made: First, in every case of anxiety in relation to the war, the child had presented previously one anxiety problem; and second, the younger children were not affected since their intellectual insight into war conditions is limited. The important observation in the report from the U.S.S.R. is that the invasion of that country has transformed the war into a personal problem for these children.

This is an important subject in all its phases, of which there are a great many, and any evidence gathered at this time will be useful in future years. First-hand knowledge gained from young children during this period will be part of the structure being built for later development.

McCULLOCH.

The Relation of Certain Anomalies of Vision and Lateral Dominance to Reading Disability. Philip W. Johnston, Ph.D., Monographs of the Society for Research in Child Development, vol. VII, no. 2 (serial no. 32), Washington, D. C., 1942, National Research Council, 147 pages.

The compilation of results of studies of the incidence of reading disabilities, together with a critical analysis of methods for testing vision and lateral dominance in relation to reading disabilities. This is a useful report, largely statistical in nature, on a subject of growing importance. Its value to the general pediatrician may be somewhat restricted, but to special workers it should be great.

McCULLOCH.